Property based Techniques for Process and Product Design

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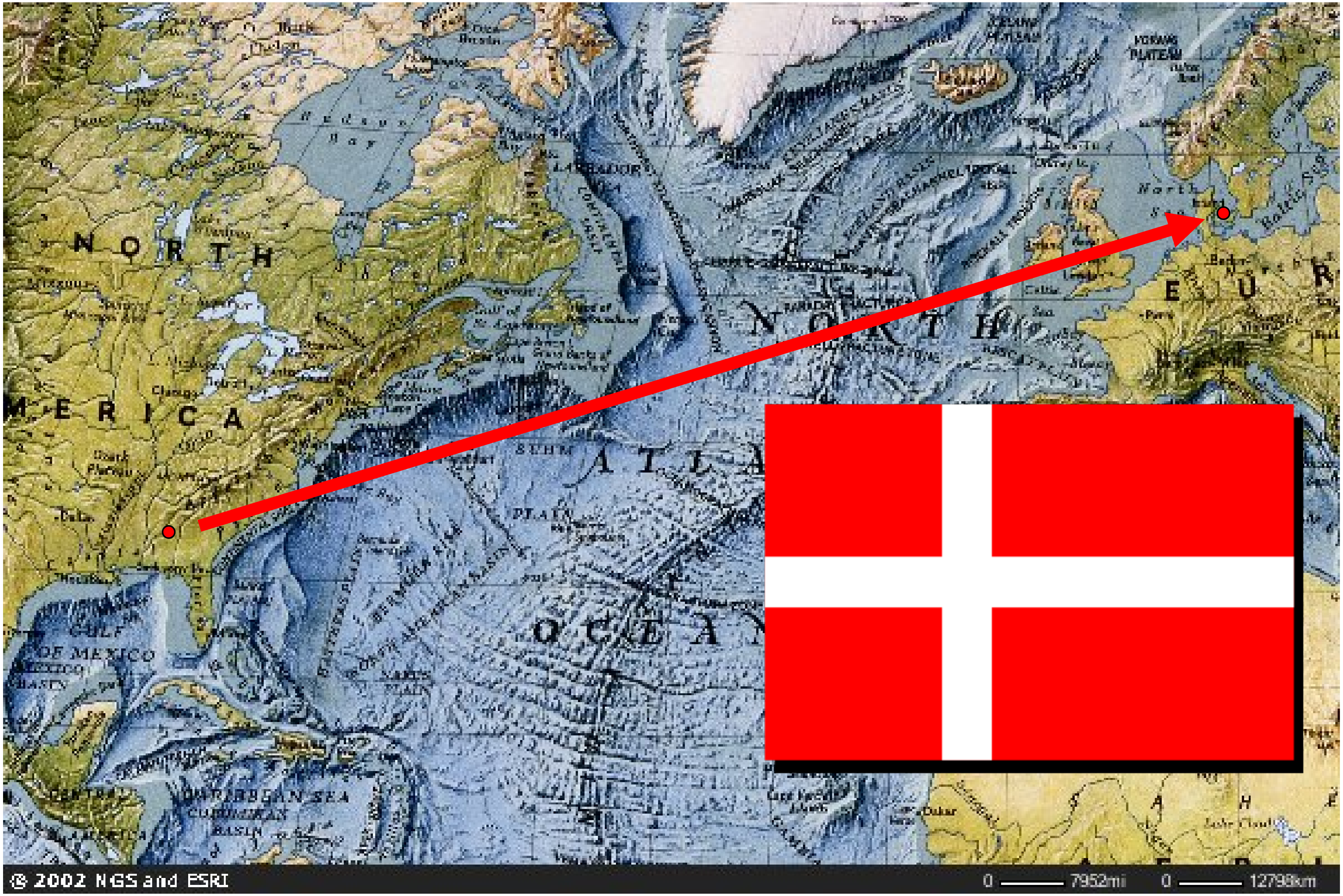
My Background

- **Background**
  - M.Sc. (Chem. Eng.), Tech. Uni. of Denmark (1999)
  - Ph.D. (Chem. Eng.), Tech. Uni. of Denmark (2003)

- **Professional Experience**
  - Associate Professor, Auburn University (2008 – present)
  - Assistant Professor, Auburn University (2004 – 2008)
  - Visiting Lecturer, Auburn University (2002 – 2003)

Where is Denmark?



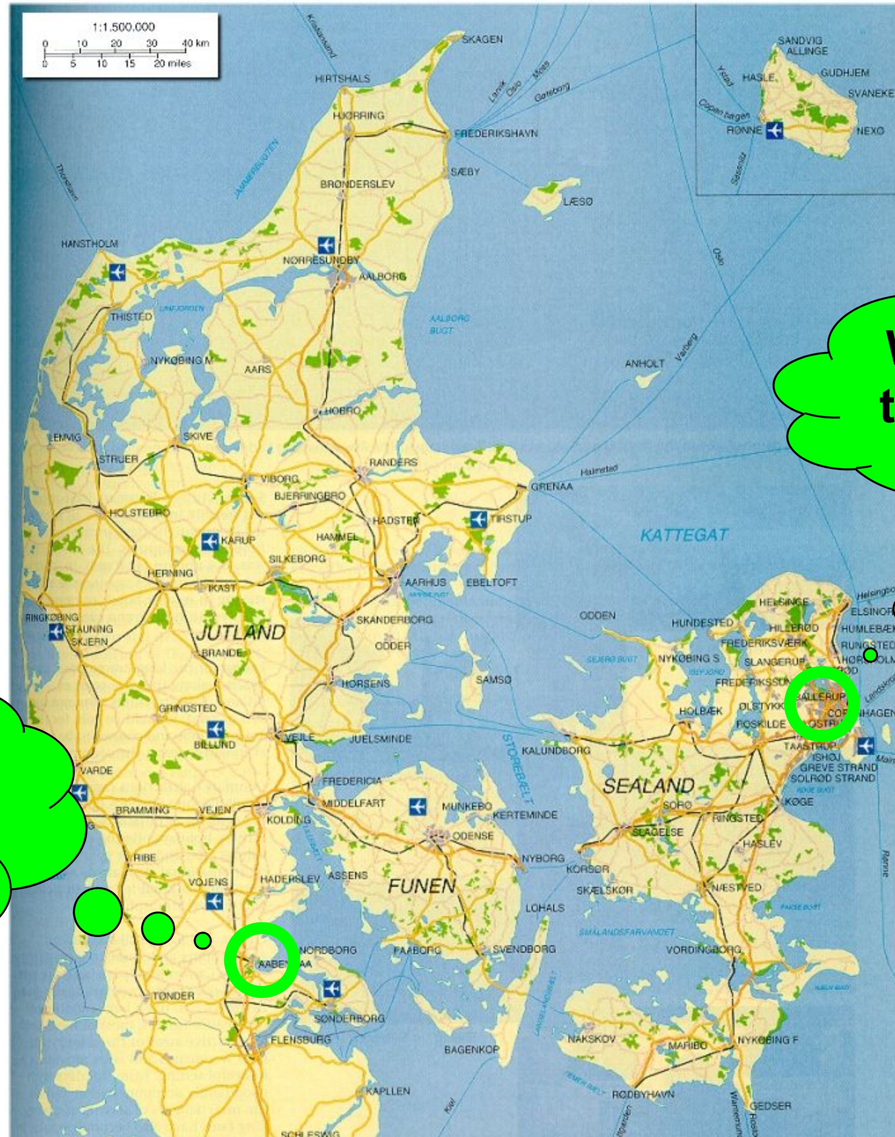
A Few Facts about Denmark

Constitutional Monarchy

A little smaller than the state of Alabama (not including Greenland)

Population approximately 5500000.

National sport – SOCCER!



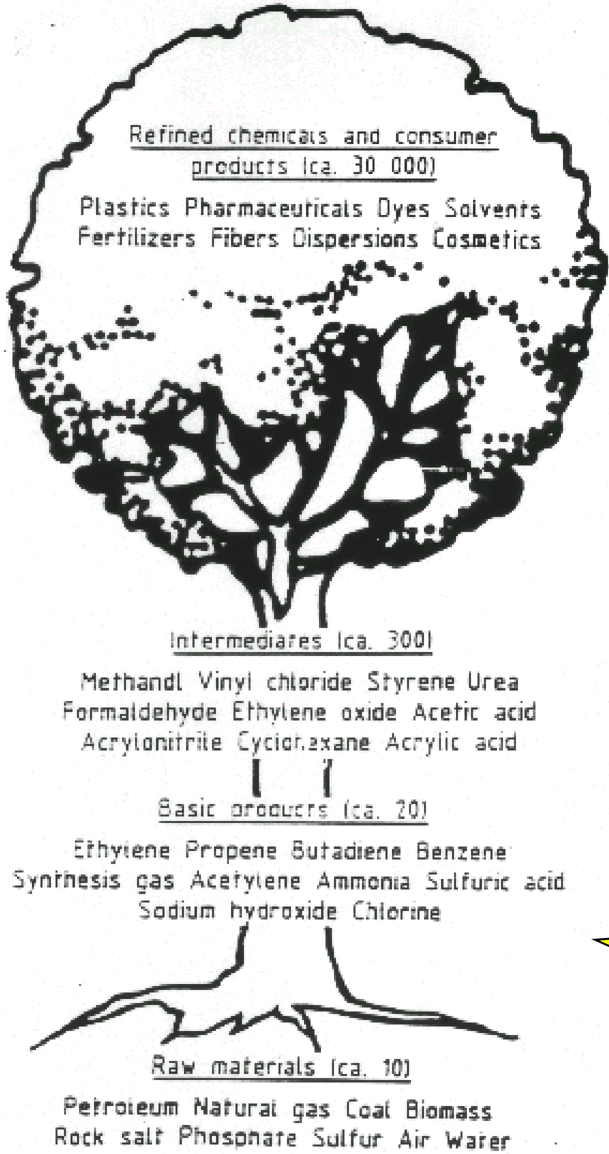
My hometown

Where I moved to go to college

My Research Interests

- **Computer Aided Process Engineering**
  - Property prediction & CAMD for solvent selection/design
  - Process modeling and simulation
- **Process/Product Synthesis and Design**
  - Develop novel efficient methods for emerging problems
  - Develop strategies for simultaneous solution
  - Systematic identification/generation of alternatives
- **Process Integration and Optimization**
  - Application of holistic methods to ensure sustainability
  - Fuels reforming and biorefinery optimization

Challenges and Motivation



Design Objectives – Identify:

- Important fruits (products)
- Optimal path to reach them
- Feasibility of the process
- Control structure
- Ressource conservation strategies
- Environment, health and safety issues

Highly complex problems due to interactions between them!!

General Design Problem 1:2

Process / Product Synthesis / Design Problem

$$F_{OBJ} = \min\{C^T \cdot y + f(x)\}$$

$$\begin{aligned} \text{s.t.}\quad & h_1(x, y) = 0 \\ & h_2(x, y) = 0 \\ & g_1(x) > 0 \\ & g_2(x, y) > 0 \\ & B \cdot y + C \cdot x > d \end{aligned}$$

- Objective Function
- Process/Product Model
- Equality and Inequality Constraints
- Structural Constraints

Conventional Solutions

A. Heuristic / knowledge-based
Satisfy only the constraints.
Generates feasible solutions.

B. Mathematical Optimization
Solve the objective function including the process model

General Design Problem 2:2

Process / Product Synthesis / Design Problem

$$F_{OBJ} = \min\{C^T \cdot y + f(x)\}$$

$$\begin{aligned} \text{s.t.} \quad & h_1(x,y) = 0 \\ & h_2(x,y) = 0 \\ & g_1(x) > 0 \\ & g_2(x,y) > 0 \\ & B \cdot y + C \cdot x > d \end{aligned}$$

Hybrid Solution Approach

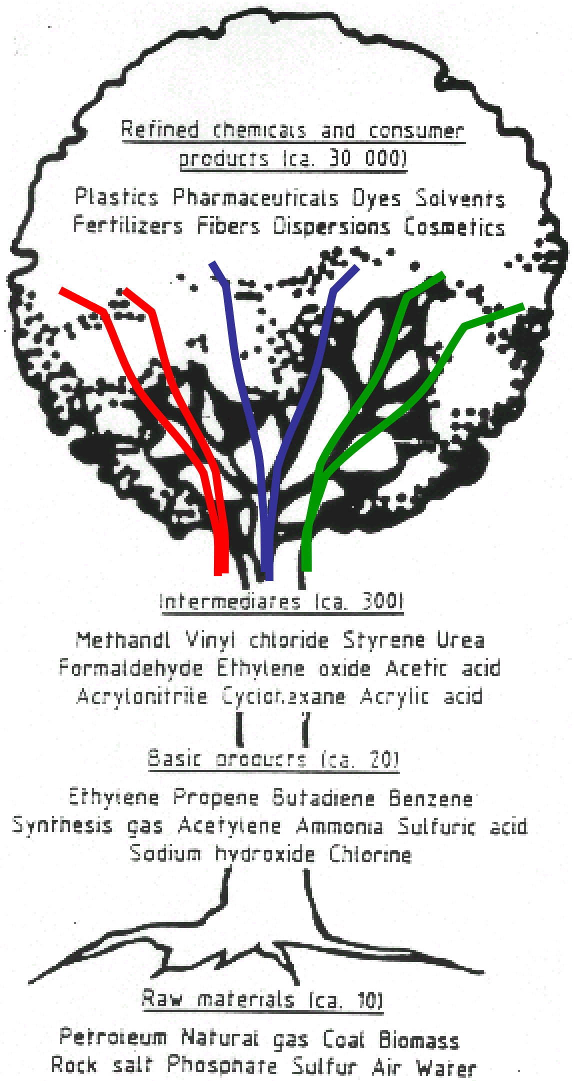
I. Define search space through heuristic or knowledge-based approach (A).

II. Solve well defined optimization problem (B).

IMPORTANT

Regardless of problem type a process model is needed and it is the model type and validity ranges that defines the application range of the solution.

Roles of Property Models 1:3



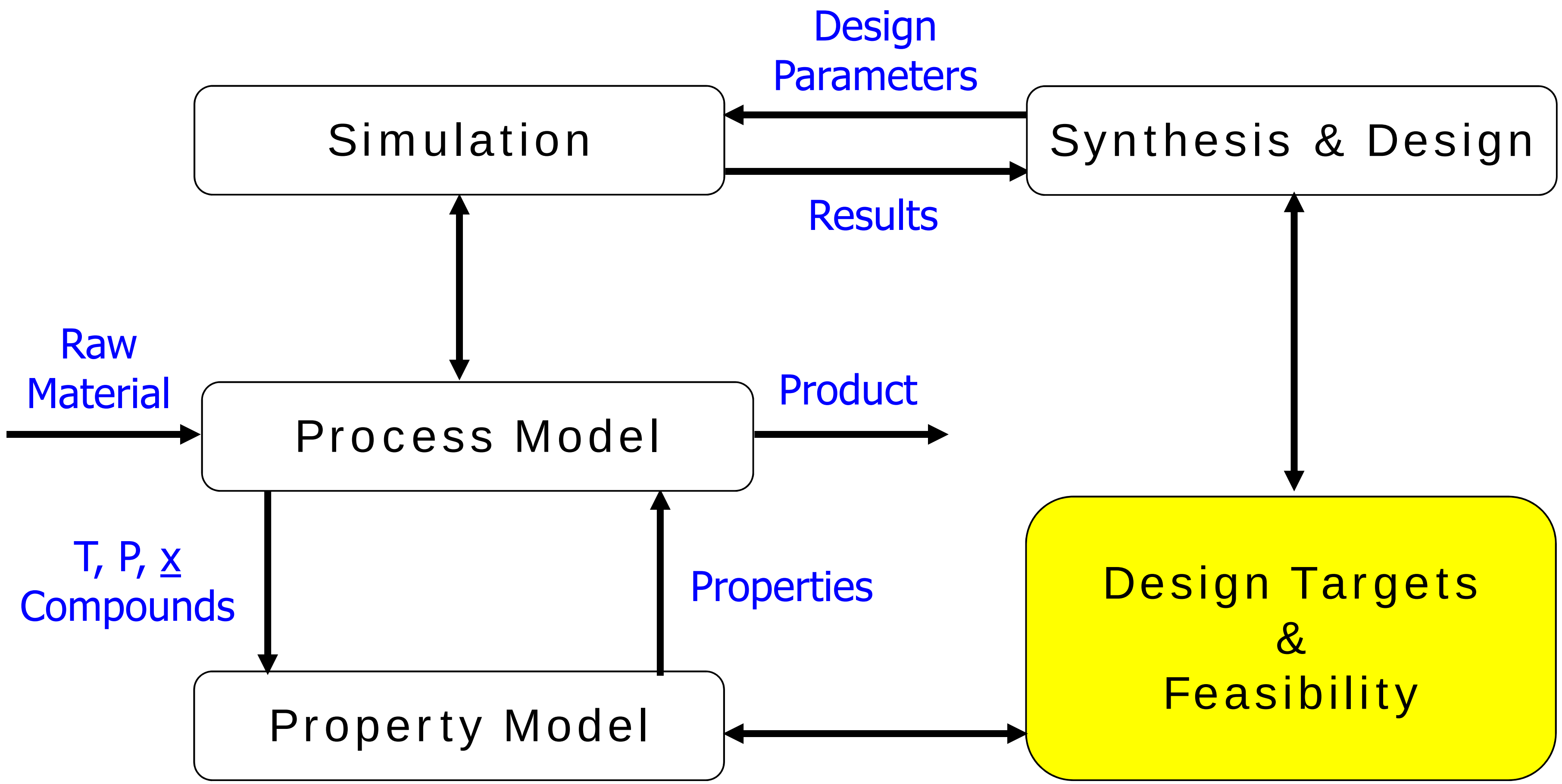
Constitutive Model

Constitutive Model

Constitutive Model

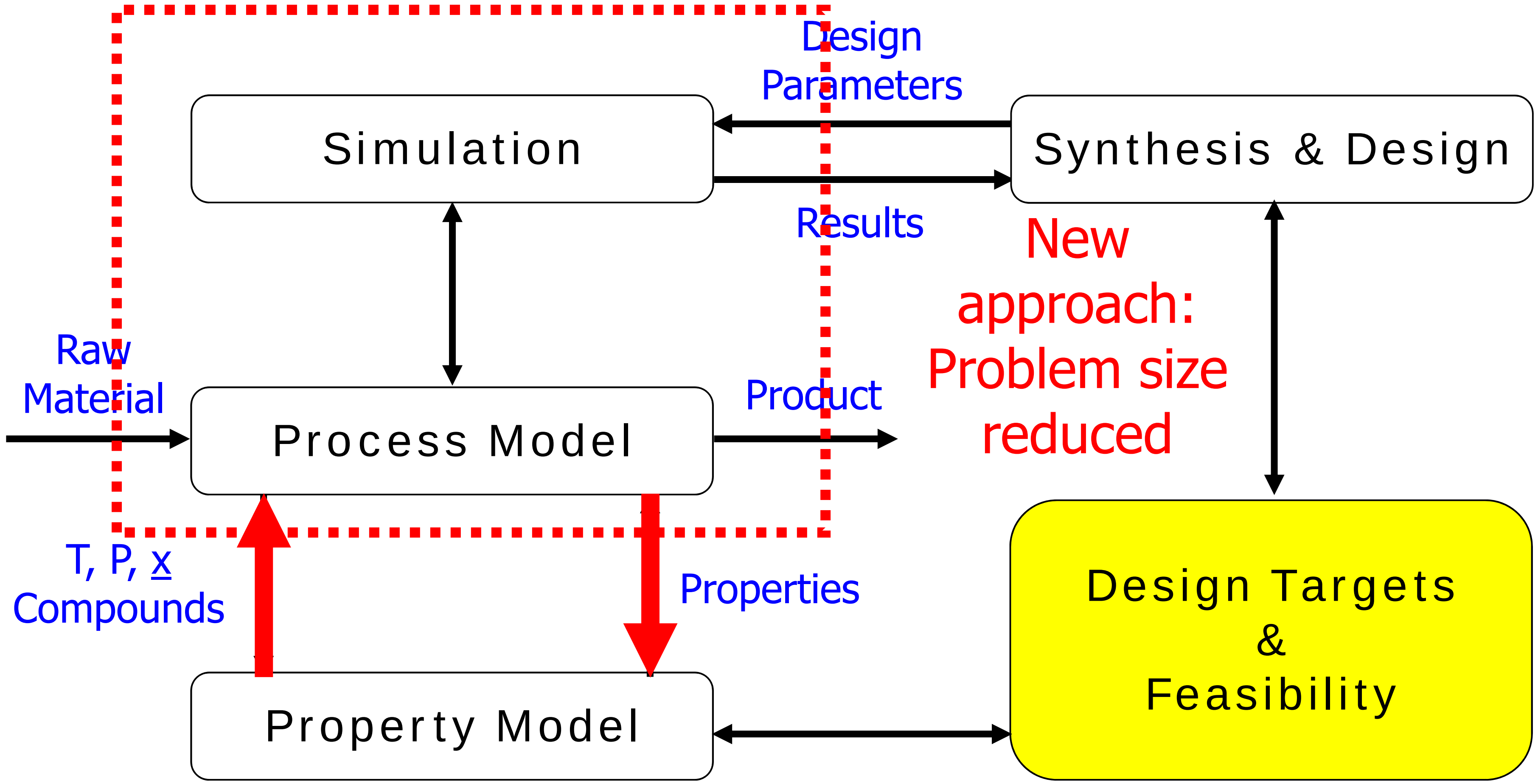
- **Choice of a constitutive model implicitly defines the search space**
- **Do we know enough to derive a single model?**
- **Can we solve simulation and/or optimization problems with multiple constitutive models representing the same variable?**

Roles of Property Models 2:3



1. Service Role for Process Model
2. Service & Advice Role for Process Model

Roles of Property Models 3:3



Compounds needed only by property model

Service, Advice & Solve Role for Process Model

Targeted Design Techniques

- **Reverse Problem Formulation Methodology**
  - Computationally efficient solution strategy
  - Targets optimal solution prior to complex calculations
  - Capable of identifying all alternatives
  - Framework enables optimum use of all model details
  - Relieves inherently iterative nature of design

Reverse Problem Formulation

Process Model

Balance and Constraint Equations (Mass, Energy, Momentum)

Constitutive Equations (Phenomena model - Function of Intensive Variables)

Balance and Constraint Equations

Identification of design targets by solution of decoupled model

REVERSE SIMULATION

DESIGN TARGETS (Constitutive Variables)

Match design targets and identify corresponding intensive variables

REVERSE PROPERTY PREDICTION

Constitutive Equations

As long as the targets are matched, the balance equations are also satisfied and do NOT need to be solved again

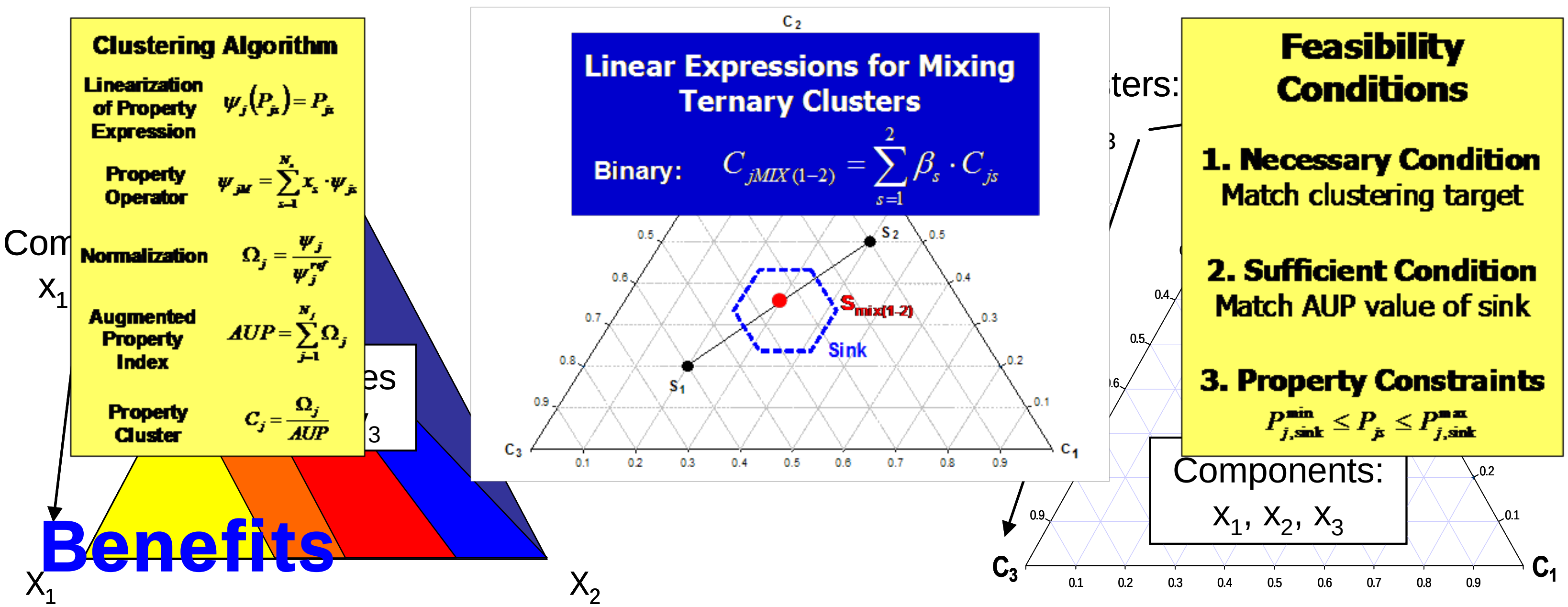
Property Based Design

- **Why Design Based on Properties?**
  - Many processes driven by properties NOT components
  - Performance objectives often described by properties
  - Often objectives can not be described by composition
  - Product/molecular design is based on properties
  - Insights hidden by not integrating properties directly

- **Property Clusters**
  - Extension to existing composition based methods
  - Reduces dimensionality of problem
  - Enables visualization of problem
  - Property estimation in molecular design via GC
  - Unifying framework for simultaneous solution

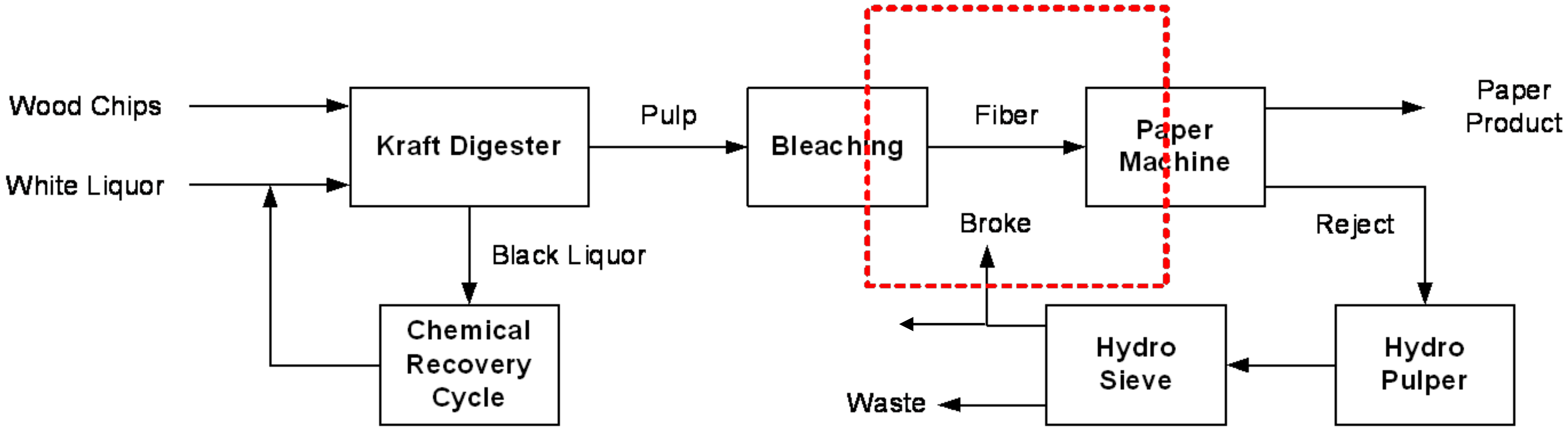
Methods

- **Property Clustering**
  - Conserved surrogate properties described by property operators, which have linear mixing rules, even if the operators themselves are nonlinear
  - Deconstructs the design problem into a Euclidean vector in the cluster domain and a scalar called the Augmented Property Index (AUP)



- **Benefits**
  - Provides the ability to link different scales
  - Can handle combinatorial intensive problems
  - Universal in application

Example 1: Process Design



Stream Characterization

1. Objectionable Material (OM)
2. Absorption coefficient (k)
3. Reflectivity (R_∞)

Given Information

1. Property and flow data for fibers and broke
2. Paper machine feed condition constraints

Papermaking Fiber Recycle 1:3

Property	Operator	Fibers	Broke	Paper machine
OM (mass fraction)	OM	0.000	0.115	0.00 – 0.02
k (m^2/g)	k	0.0012	0.0013	0.00115 – 0.00125
R_∞	$(R_\infty)^{5.92}$	0.82	0.90	0.80 – 0.90
Flowrate (ton/hr)	-----	100	30	100 – 105

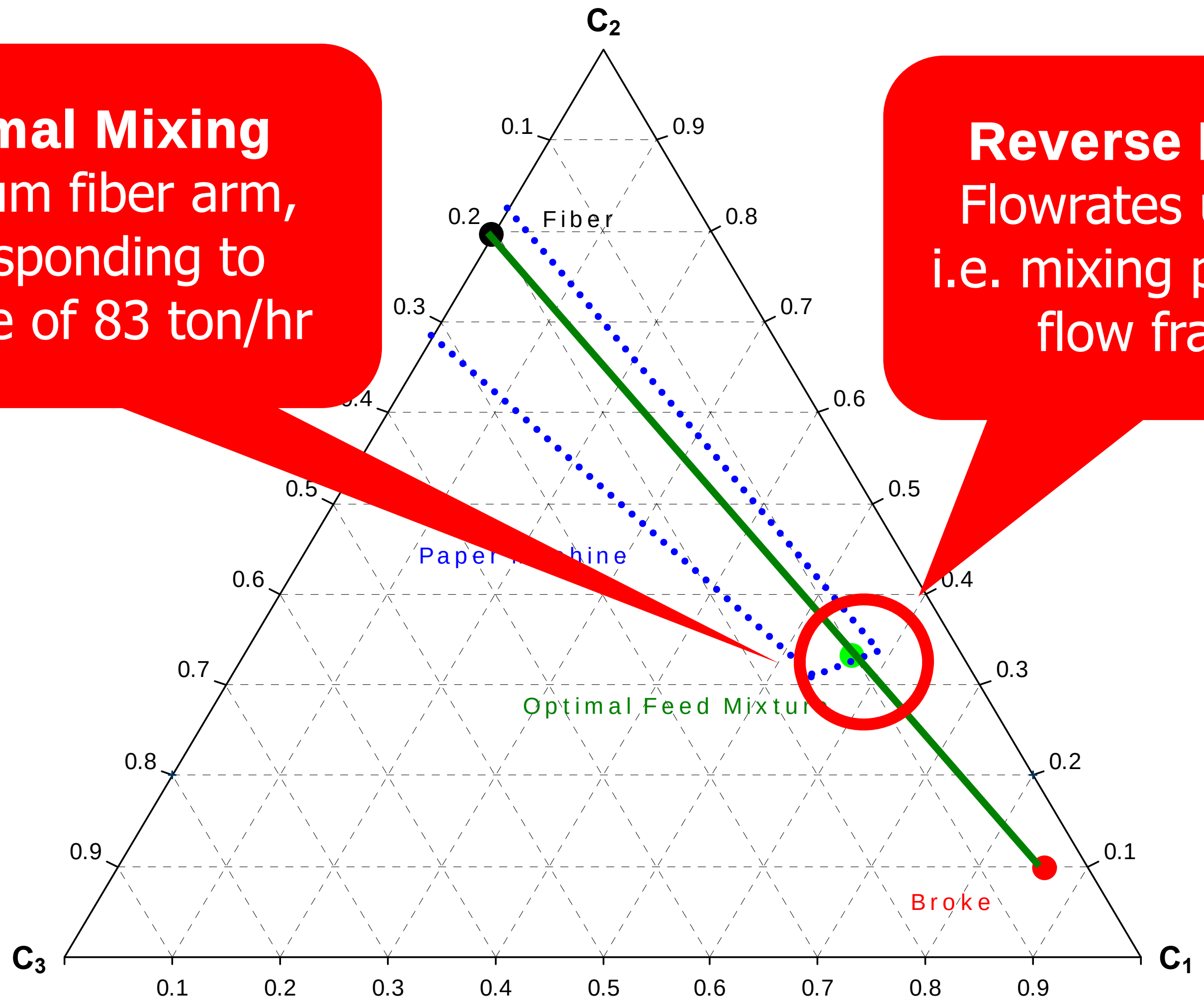
Minimum Fiber Usage
Assuming full recycle and interception capabilities, the minimum fiber usage will be 70 ton/hr

Solution Strategies
1. Direct recycle
2. Interception and recycle

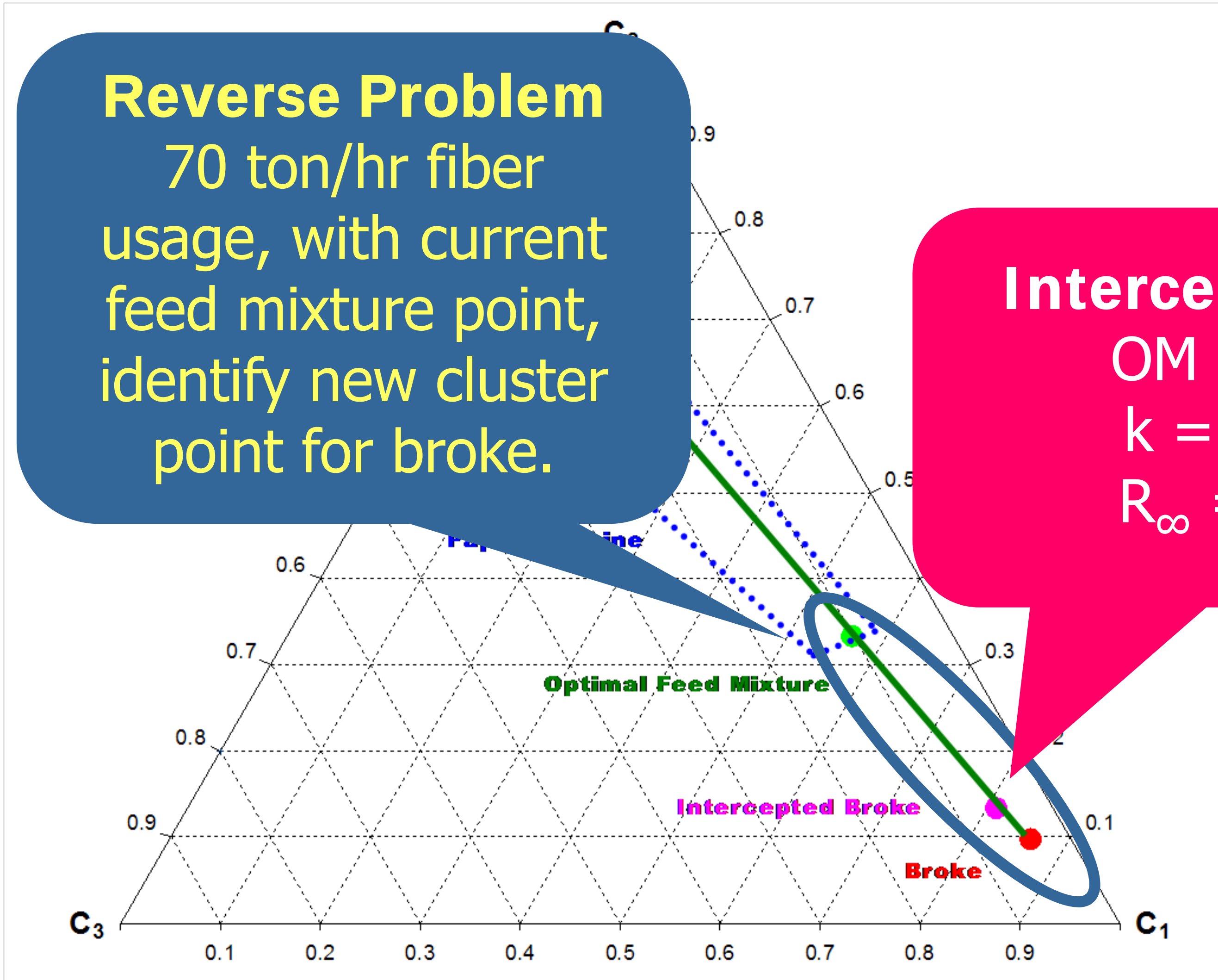
Papermaking Fiber Recycle 2:3

Optimal Mixing
Minimum fiber arm, corresponding to flowrate of 83 ton/hr

Reverse Problem
Flowrates unknown, i.e. mixing point yields flow fractions



Papermaking Fiber Recycle 3:3



Reverse Problem
70 ton/hr fiber usage, with current feed mixture point, identify new cluster point for broke.

Intercepted Broke
OM = 0.067
k = 0.0011
R_{∞} = 0.879

Molecular Clusters 1:2

Process Property Operators

$$\psi_j^P = \sum_{s=1}^{N_s} x_s \cdot P_{js}$$

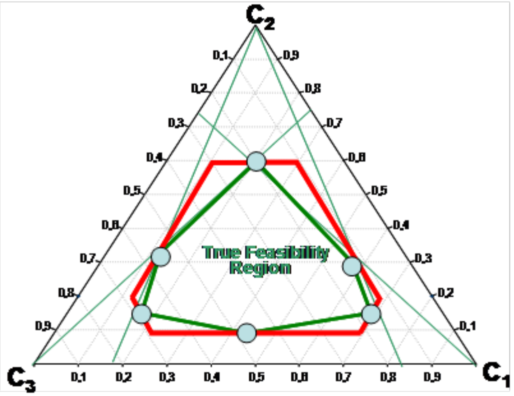
Linear Expression for Mixing 2 Ternary Clusters

$$C_{jMIX} = \sum_{s=1}^{N_s} \beta_s \cdot C_{js}$$

$$\Omega_j = \frac{\psi_j}{\psi_j^{ref}}$$

$$AUP = \sum_{j=1}^{N_j} \Omega_j$$

$$C_j = \frac{\Omega_j}{AUP}$$



Molecular Property Operators

$$\psi_j^M = \sum_{g=1}^{N_g} n_g \cdot P_{jg}$$

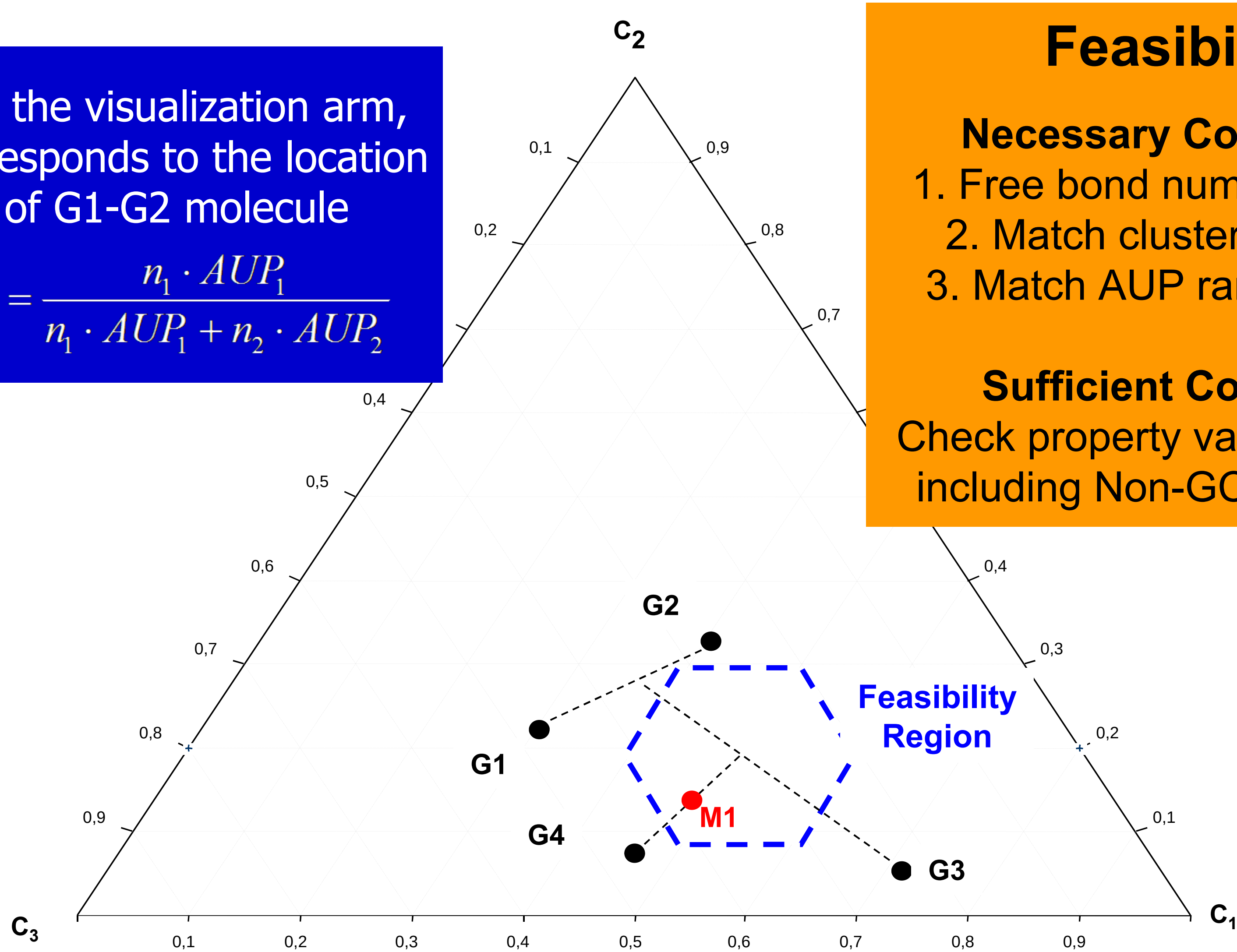
G_1 and G_2, are added linearly on the ternary diagram. The location of β_1, corresponds to the location of G_1-G_2 molecule

$$\beta_1 = \frac{n_1 \cdot AUP_1}{n_1 \cdot AUP_1 + n_2 \cdot AUP_2}$$

Molecular Clusters 2:2

β_1, the visualization arm, corresponds to the location of G1-G2 molecule

$$\beta_1 = \frac{n_1 \cdot AUP_1}{n_1 \cdot AUP_1 + n_2 \cdot AUP_2}$$



Feasibility

Necessary Conditions

1. Free bond number is zero.
2. Match clustering target
3. Match AUP range of sink

Sufficient Condition

Check property value with sink including Non-GC properties

Example 2: Molecular Synthesis

- **Blanket Wash Solvent Design**
  - Solved as MINLP by Sinha and Achenie (2001)
- **Problem Statement**
  - Design blanket wash solvent for phenolic resin printing ink
  - Molecules designed from 7 possible groups, with a max. chain length of 7 groups

Property	Lower Bound	Upper Bound
Hv (kJ/mol)	20	60
Tb (K)	350	400
Tm (K)	150	250
VP (mmHg)	100	---
R^{ij}	0	19.8

Blanket Wash Solvent 1:7

- Visualization limits problem to three properties
- Heat of vaporization, boiling and melting temperatures are used, with vapor pressure and solubility used as final screening properties

Property Prediction (GCM)

$$\Delta H_v - h_{vo} = \sum_i g_i \cdot h_{vi}$$

$$T_b = t_{bo} \cdot \ln \sum_i g_i \cdot t_{b1_i}$$

$$T_m = t_{mo} \cdot \ln \sum_i g_i \cdot t_{m1_i}$$

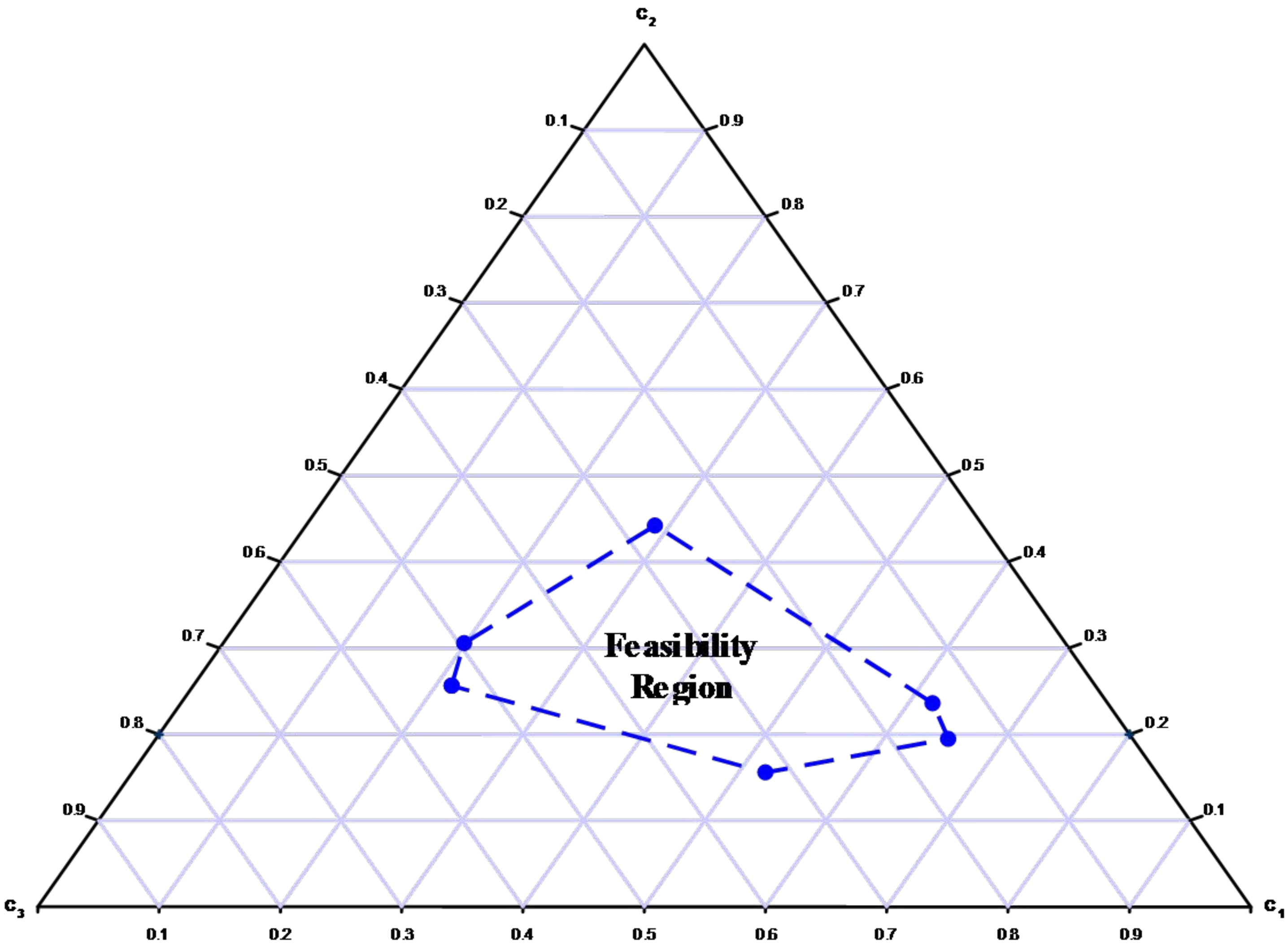
Molecular Property Operators

$$\Delta H_v - h_{vo} = \sum_i n_g \cdot h_{v1} \quad , \Psi^{ref} = 20$$

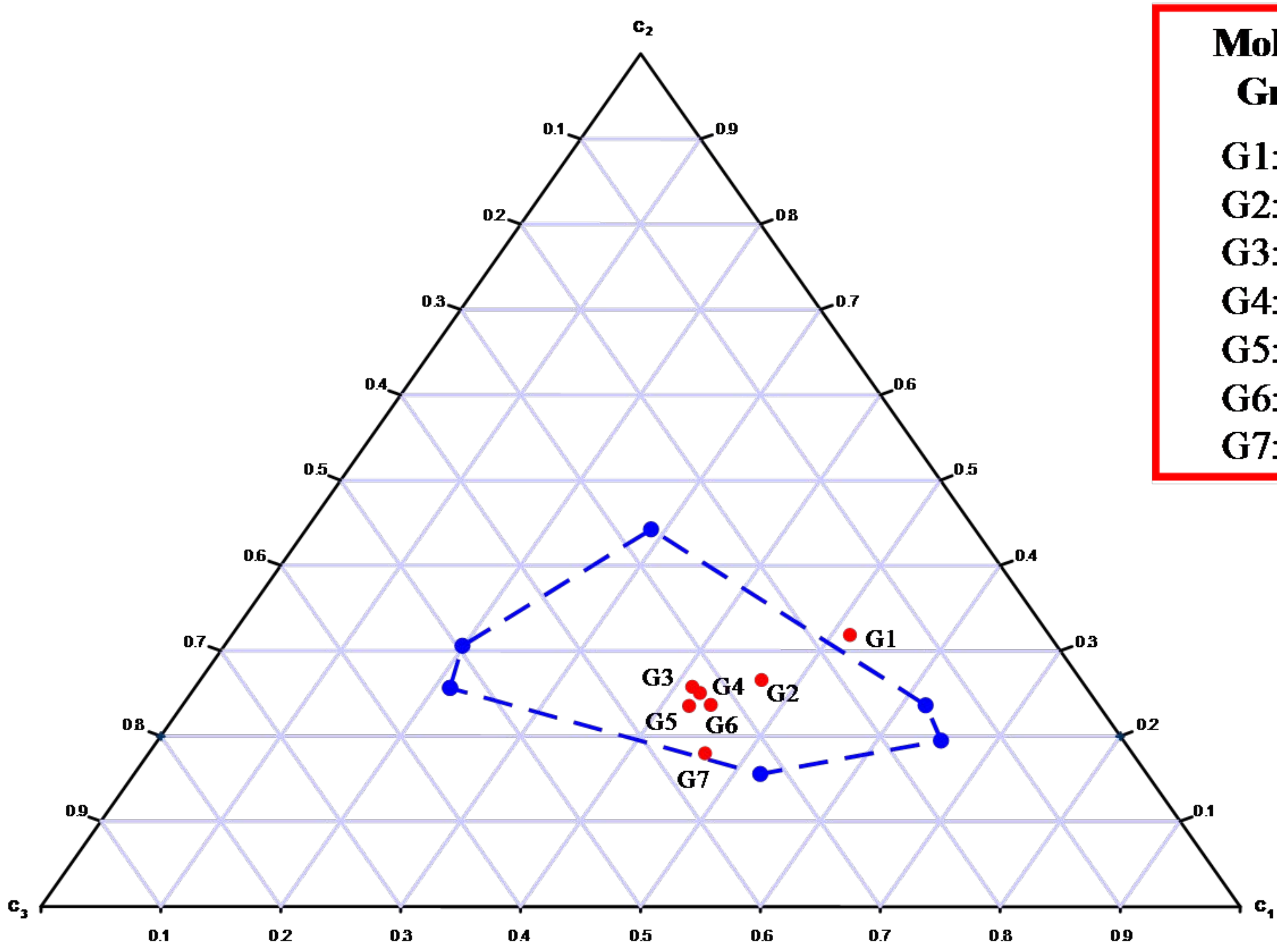
$$\exp\left(\frac{T_b}{t_{bo}}\right) = \sum_{g=1}^{N_g} n_g \cdot t_{b1} \quad , \Psi^{ref} = 100$$

$$\exp\left(\frac{T_m}{t_{mo}}\right) = \sum_{g=1}^{N_g} n_g \cdot t_{m1} \quad , \Psi^{ref} = 7$$

Blanket Wash Solvent 2:7



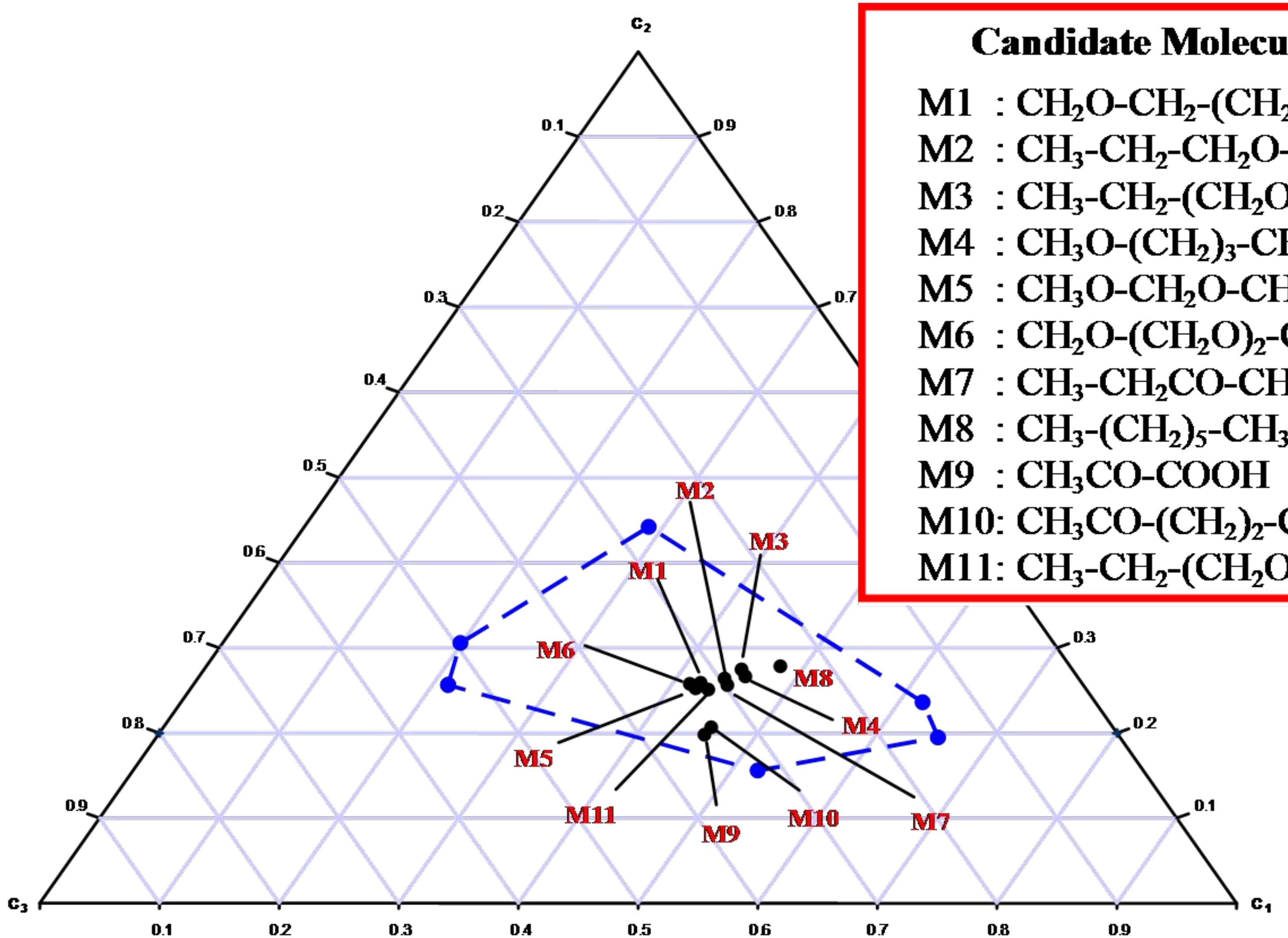
Blanket Wash Solvent 3:7



Molecular Groups

G1: CH_3
G2: CH_2
G3: CH_2O
G4: CH_3O
G5: CH_2CO
G6: CH_3CO
G7: COOH

Blanket Wash Solvent 4:7



Candidate Molecules

M1 : $CH_2O\text{-}CH_2\text{-}(CH_2O)_2$
M2 : $CH_3\text{-}CH_2\text{-}CH_2O\text{-}CH_3O$
M3 : $CH_3\text{-}CH_2\text{-}(CH_2O)_2\text{-}CH_3$
M4 : $CH_3O\text{-}(CH_2)_3\text{-}CH_3$
M5 : $CH_3O\text{-}CH_2O\text{-}CH_3O$
M6 : $CH_2O\text{-}(CH_2O)_2\text{-}CH_2O$
M7 : $CH_3\text{-}CH_2CO\text{-}CH_3$
M8 : $CH_3\text{-}(CH_2)_5\text{-}CH_3$
M9 : $CH_3CO\text{-}COOH$
M10: $CH_3CO\text{-}(CH_2)_2\text{-}COOH$
M11: $CH_3\text{-}CH_2\text{-}(CH_2O)_2$

Blanket Wash Solvent 5:7

- **Feasible formulations from Visual Synthesis**

Formulations	AUP	H_v kJ/mol	T_b K	T_m K	VP mmHg	R^{ij} MPa
M1	3.20	33.91	359.14	201.24	1117.85	10.88
M2	3.08	33.99	355.34	189.86	1240.95	15.39
M3	3.10	34.67	364.49	183.38	963.57	12.83
M4	3.17	35.81	363.09	186.26	1001.85	18.09
M5	3.47	36.15	370.61	211.95	811.54	15.82
M6	3.61	36.74	382.51	216.49	578.05	11.31
M7	3.17	35.10	354.80	193.13	1259.28	16.84
M8	3.28	38.31	379.07	175.55	638.03	19.77
~~M9~~	~~6.79~~	~~68.87~~	~~457.92~~	~~286.76~~	~~56.69~~	~~13.83~~
~~M10~~	~~7.79~~	~~78.17~~	~~494.54~~	~~297.68~~	~~16.55~~	~~12.68~~
~~M11~~	~~7.83~~	~~74.75~~	~~535.55~~	~~292.08~~	~~3.86~~	~~11.33~~

- **Application of feasibility conditions**
  - All formulations satisfy the first two necessary conditions
  - M9-M11 fail to satisfy the AUP range of the sink

Blanket Wash Solvent 6:7

- **Feasible formulations from Visual Synthesis**

Formulations	AUP	H_v kJ/mol	T_b K	T_m K	VP mmHg	R^{ij} MPa
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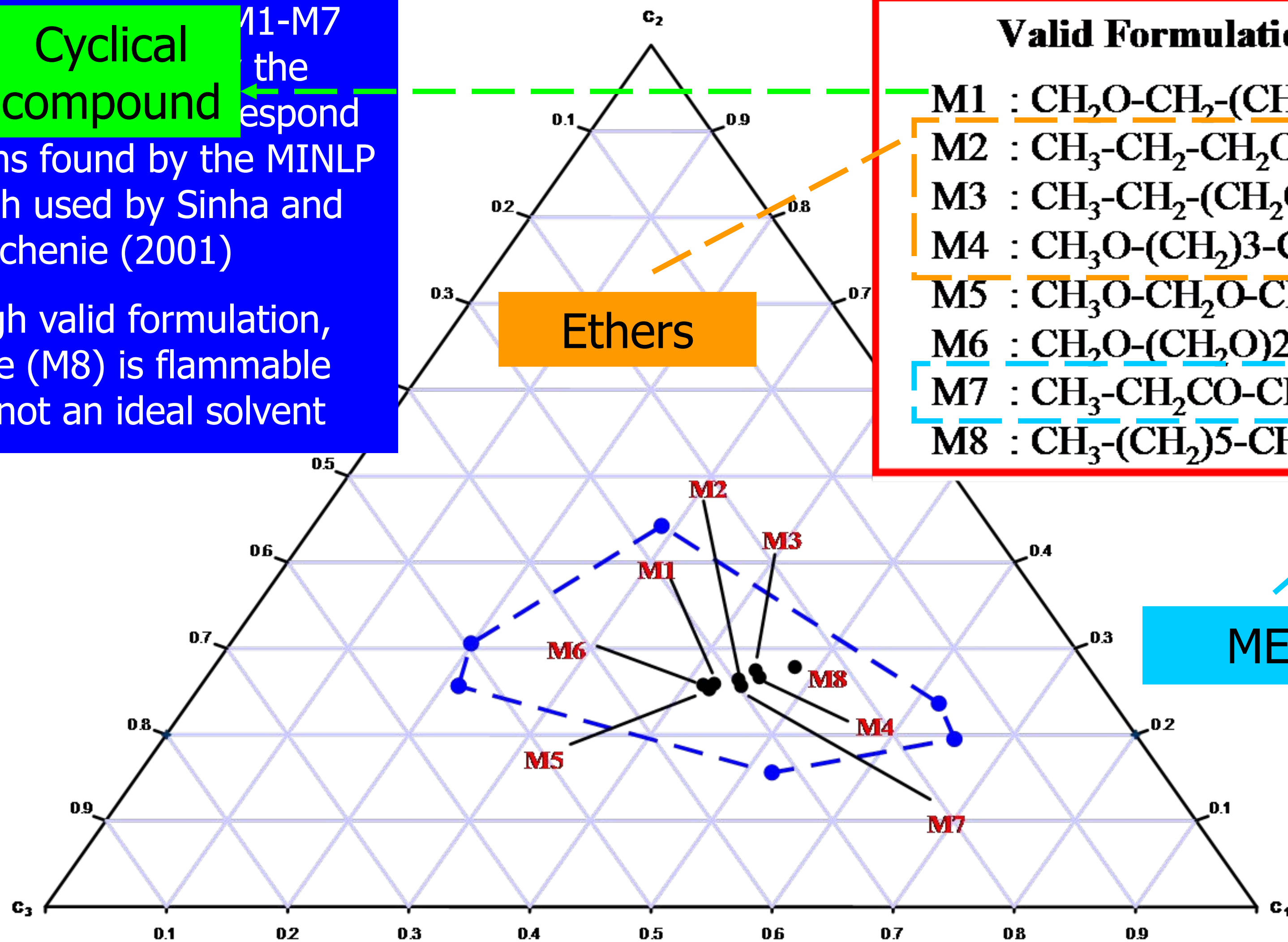
- **Application of feasibility conditions**
  - Checking property values with sink including Non-GC properties (VP, solubility), the sufficient conditions are satisfied for remaining formulations

Blanket Wash Solvent 7:7

Candid[…]M1-M7 ident[…] the develop[…]espond to solutions found by the MINLP approach used by Sinha and Achenie (2001)

Cyclical compound

Although valid formulation, heptane (M8) is flammable hence not an ideal solvent



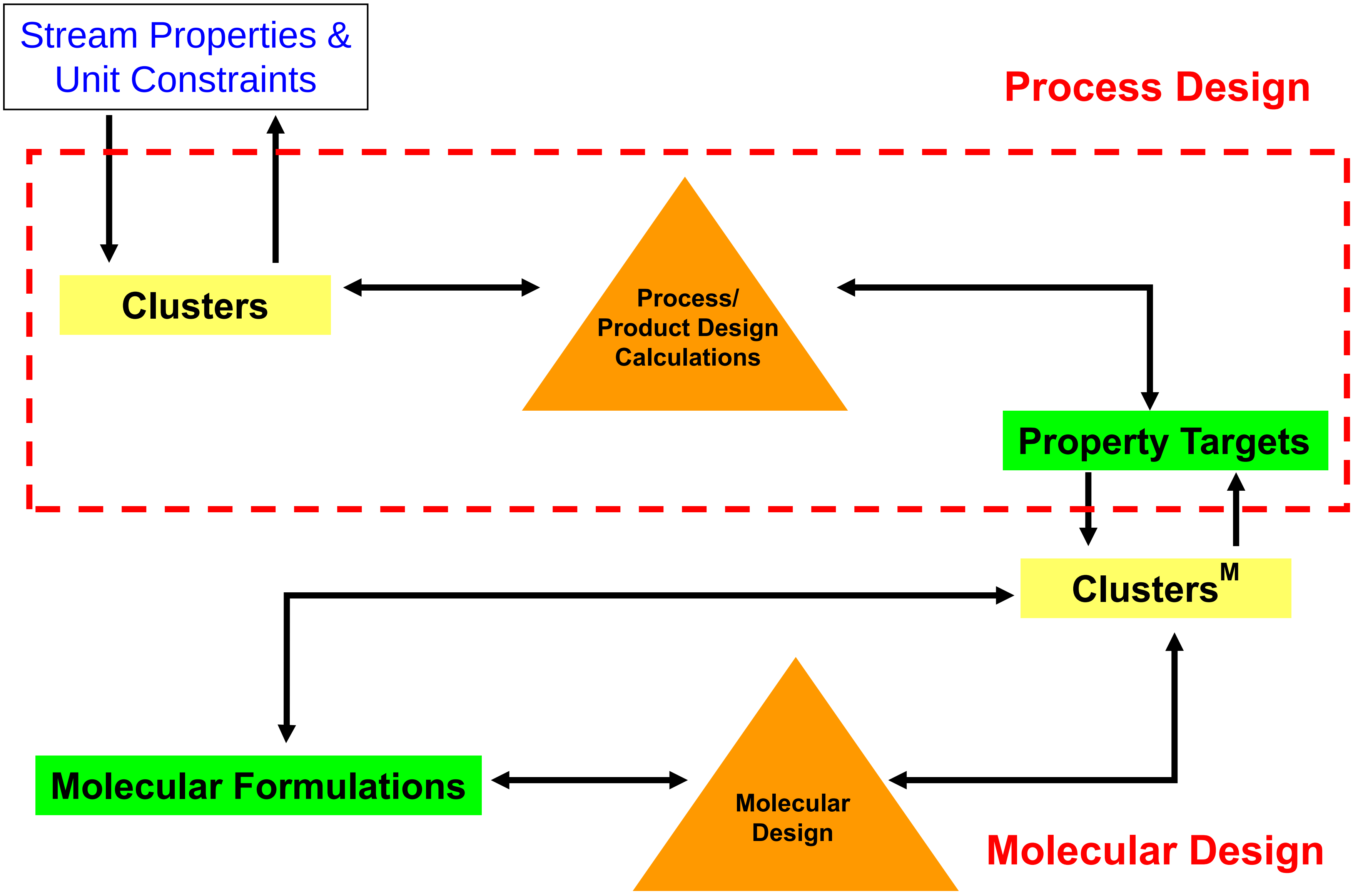
Ethers

MEK

Valid Formulations

M1 : CH_2O-CH_2-$(CH_2O)2$
M2 : CH_3-CH_2-CH_2O-CH_3O
M3 : CH_3-CH_2-$(CH_2O)2$-CH_3
M4 : CH_3O-$(CH_2)3$-CH_3
M5 : CH_3O-CH_2O-CH_3O
M6 : CH_2O-$(CH_2O)2$-CH_2O
M7 : CH_3-CH_2CO-CH_3
M8 : CH_3-$(CH_2)5$-CH_3

Integrated Design Approach



Example 3 – Integrated Design

Objective

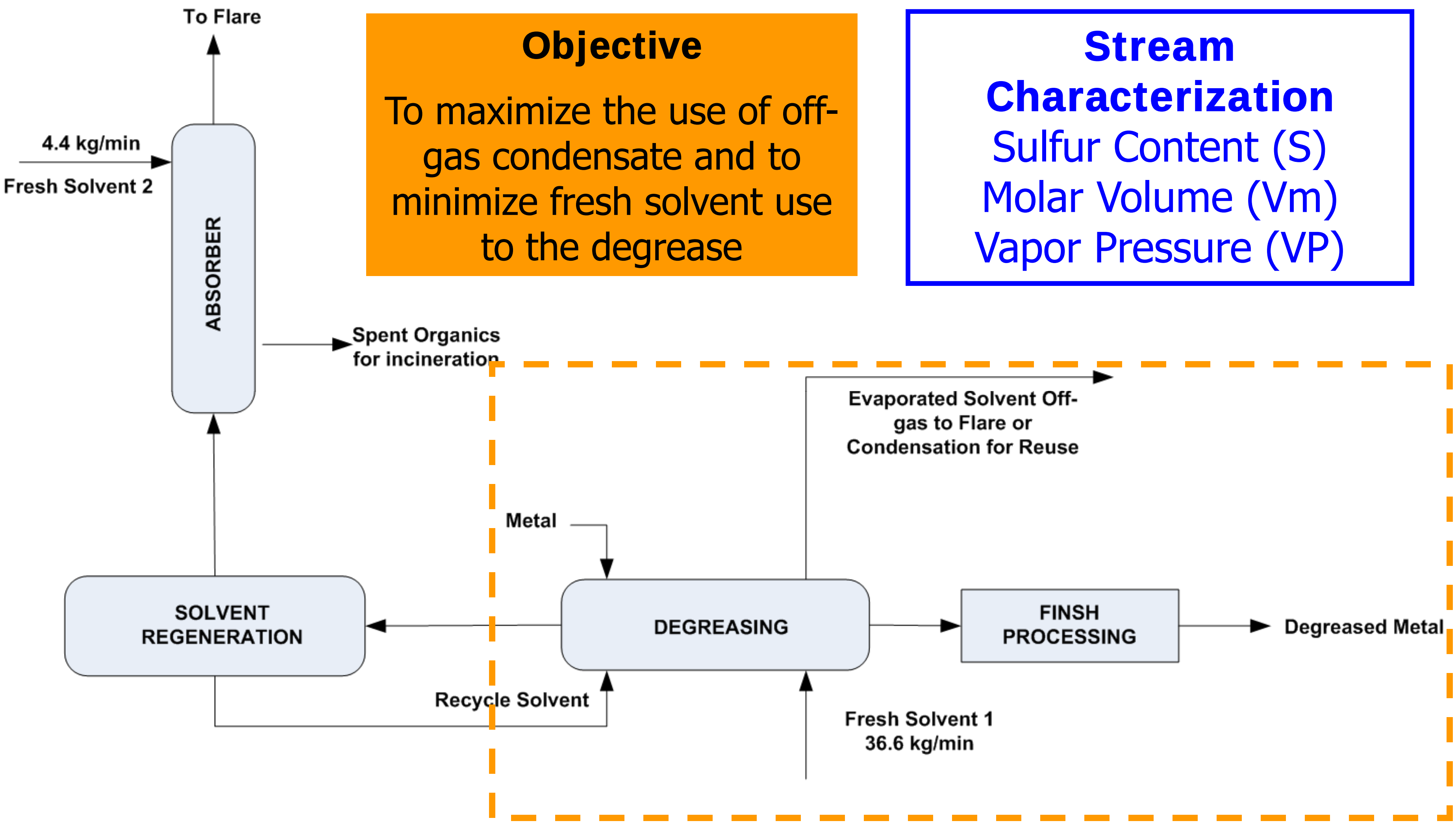
To maximize the use of off-gas condensate and to minimize fresh solvent use to the degrease

Stream Characterization

Sulfur Content (S)

Molar Volume (Vm)

Vapor Pressure (VP)



Metal Degreasing 1:9

- Degreaser Feed Constraints

Property	Lower Bound	Upper Bound
S (%)	0.00	1.00
V_m (cm^3/mol)	90.09	487.80
VP (mmHg)	1596	3040

- Property Operator Mixing Rules

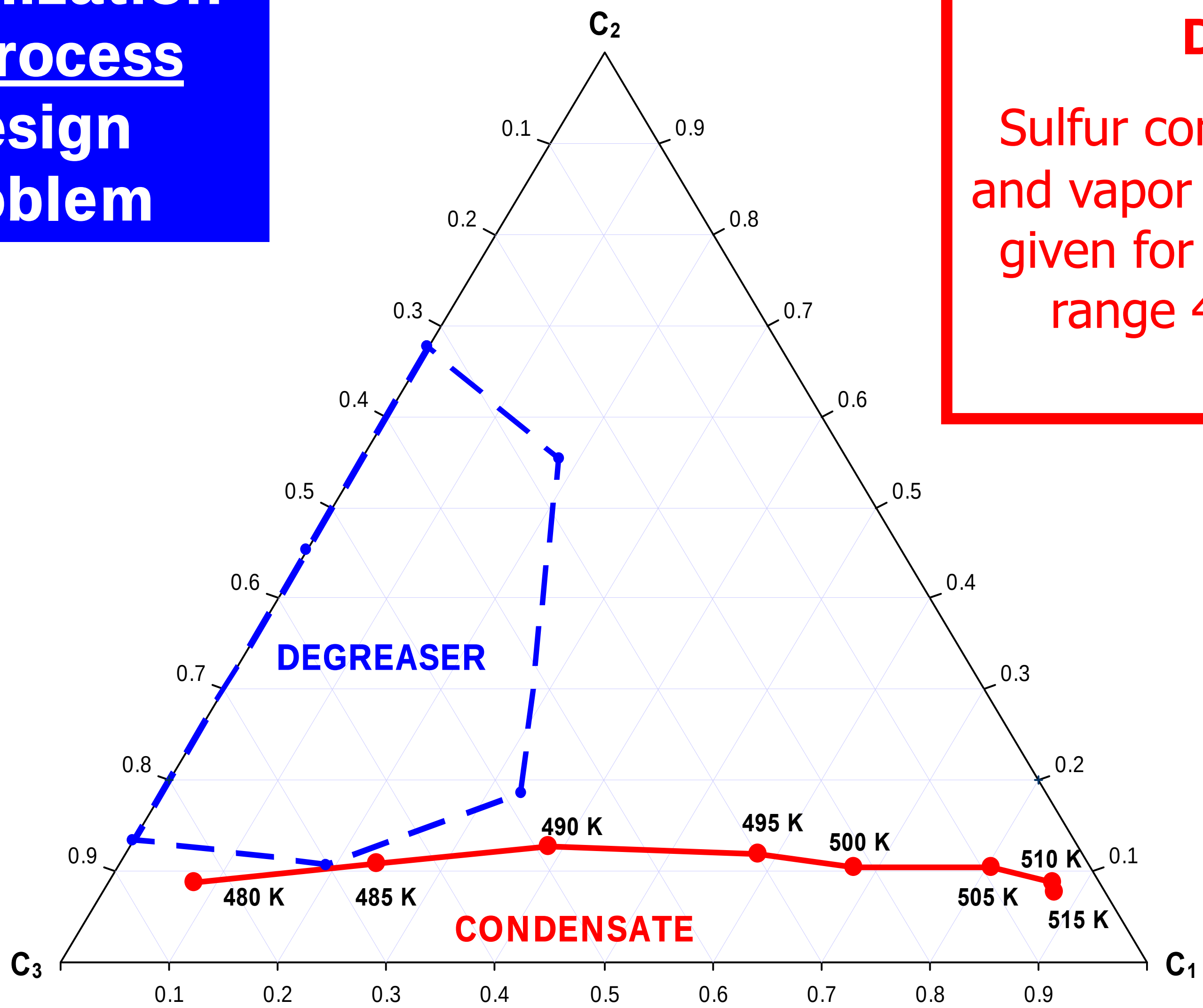
$$S_M = \sum_{s=1}^{Ns} x_s \cdot S_s \qquad , S^{ref} = 0.5 \text{ wt\%}$$

$$V_{m_M} = \sum_{s=1}^{Ns} x_s \cdot V_{m\,s} \qquad , V_m^{ref} = 80 \text{ cm3/mol}$$

$$VP_M^{1.44} = \sum_{s=1}^{Ns} x_s \cdot VP_s^{1.44} \qquad , VP^{ref} = 760 \text{ mmHg}$$

Metal Degreasing 2:9

Visualization of <u>Process</u> Design Problem



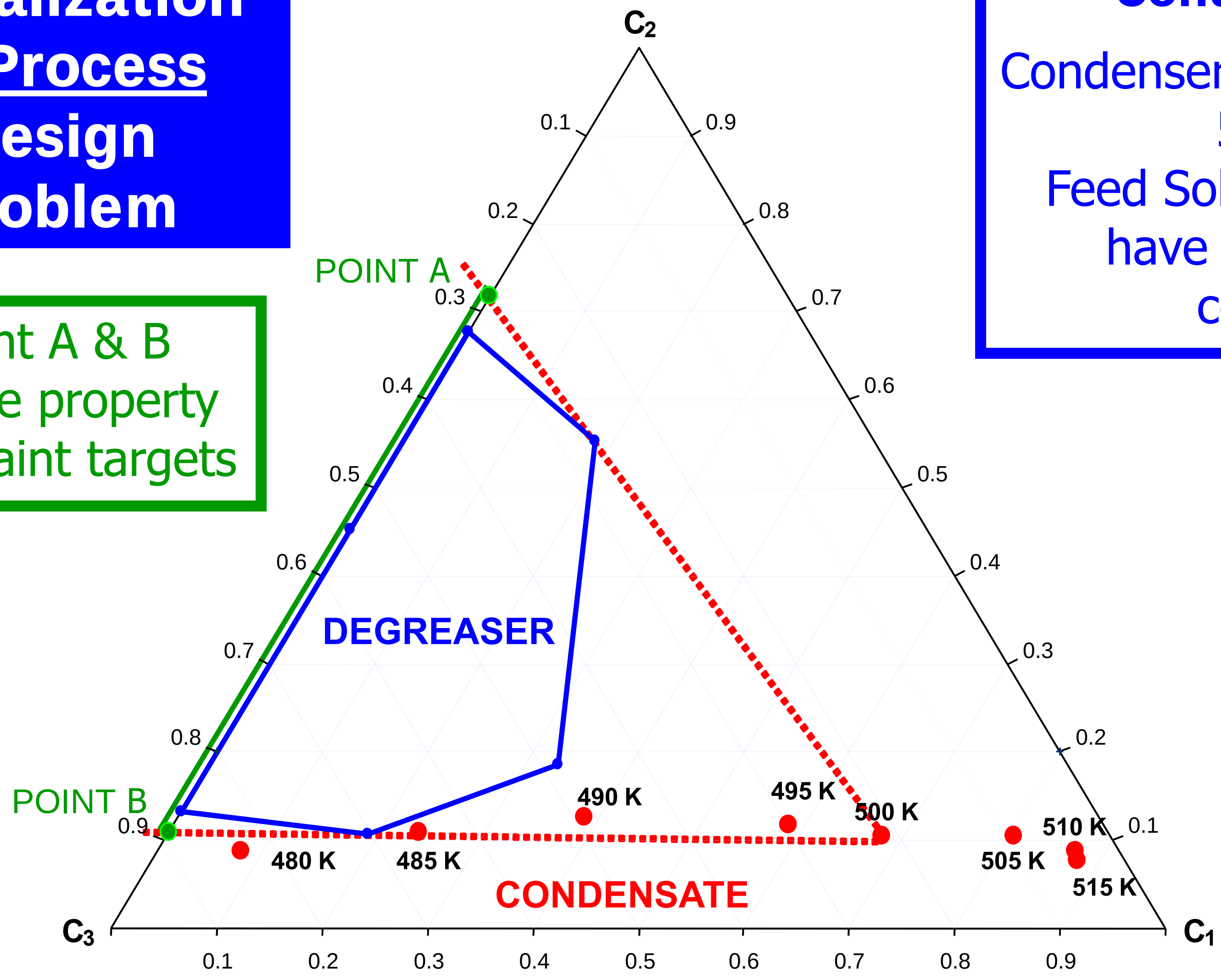
VOC Condensation Data

Sulfur content, density and vapor pressure data given for temperature range 480K-515K

Metal Degreasing 3:9

Visualization of <u>Process</u> Design Problem

Point A & B dictate property constraint targets

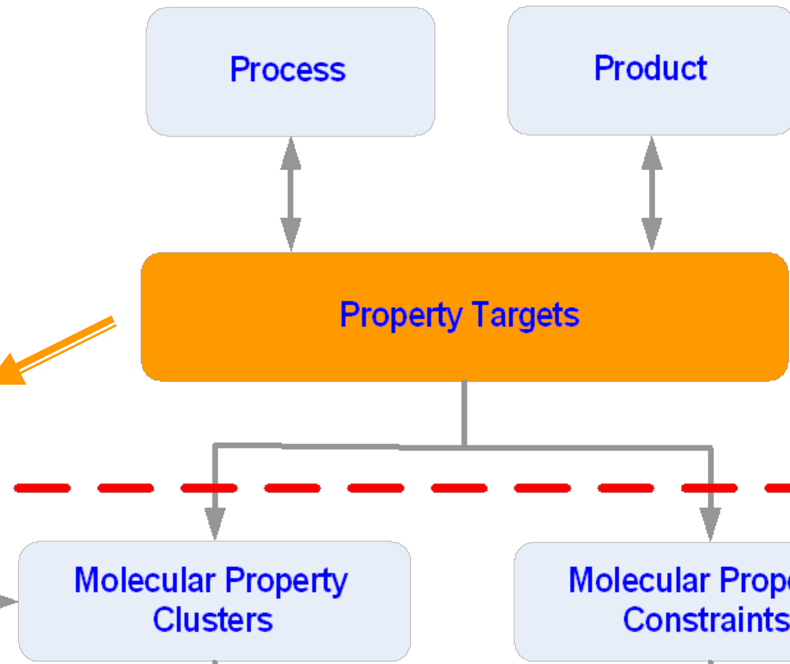


Conditions

Condenser operates @ 500 K

Feed Solvent must have zero sulfur content

Metal Degreasing 4:9



Values from Process Design Visual Solution

S (%)	V_m (cm^3/mol)	VP (mmHg)
0	102.09	1825.37
0	720.75	3878.66

Property^M Cluster Framework

Molecular Property Constraints

H_v (kJ/mol)	V_m (cm^3/mol)	VP (mmHg)
50	102.09	1825.37
100	720.75	3878.66

Metal Degreasing 5:9

Property Prediction (GCM)

$$\Delta H_v = h_{vo} + \sum_i n_i \cdot h_{v1_i}$$

$$V_m = d + \sum_i n_i \cdot v_{1_i}$$

$$T_{bp} = t_{bo} \cdot \ln \sum_i n_i \cdot t_{b1}$$

$$\log_{10} VP = 5.58 - 2.7\left(\frac{T_{bp}}{T}\right)^{1.7}$$

Non-GC Property

Molecular Property Operators

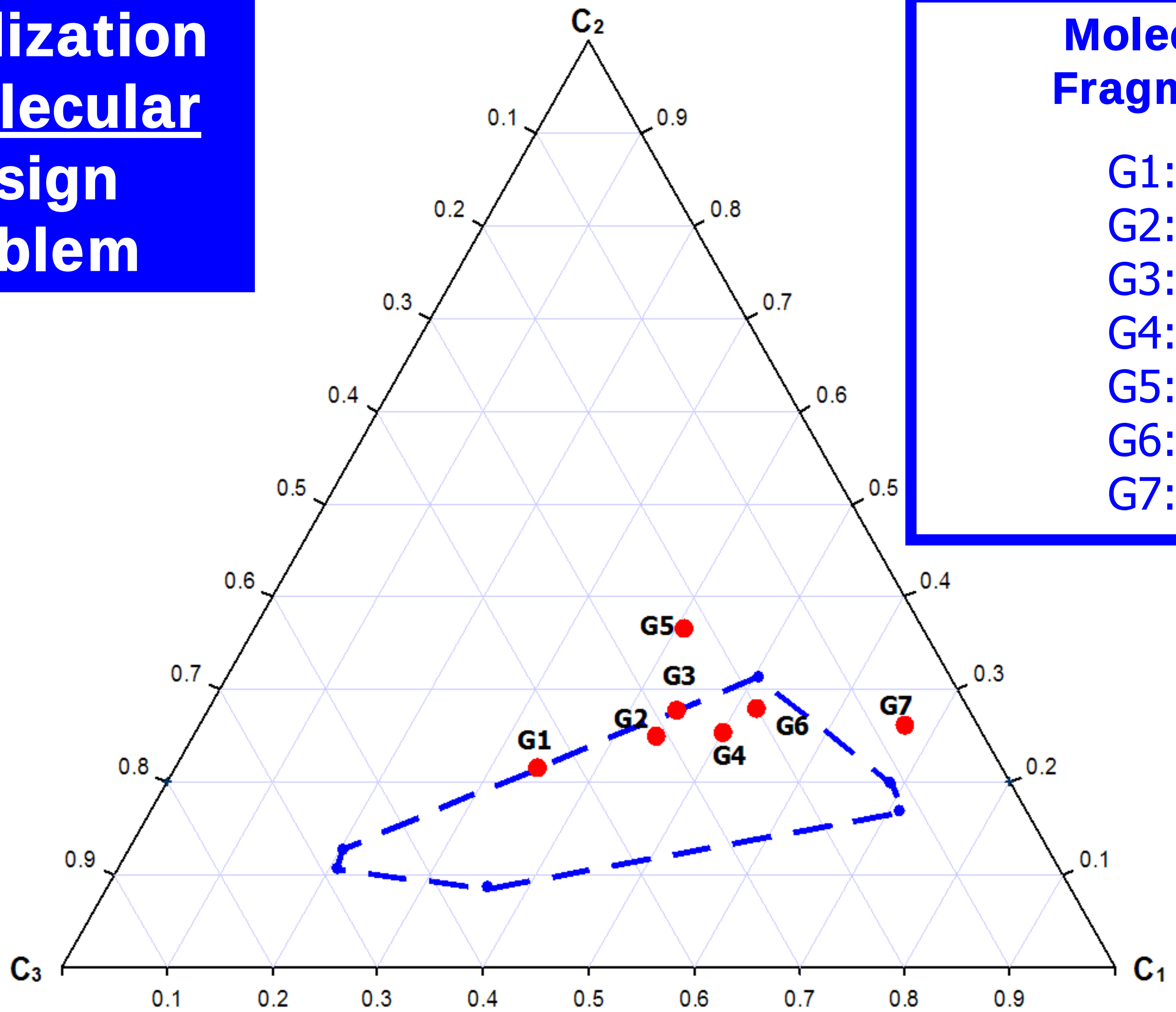
$$\Delta H_v - h_{vo} = \sum_{g=1}^{N_g} n_g \cdot h_{v1_g} \quad , \psi^{ref} = 20$$

$$V_m - d = \sum_{g=1}^{N_g} n_g \cdot v_{1_g} \quad , \psi^{ref} = 100$$

$$\exp\left(\frac{T_{bo}}{t_{bo}}\right) = \sum_{g=1}^{N_g} n_g \cdot t_{b1_g} \quad , \psi^{ref} = 7$$

Metal Degreasing 6:9

Visualization of <u>Molecular</u> Design Problem

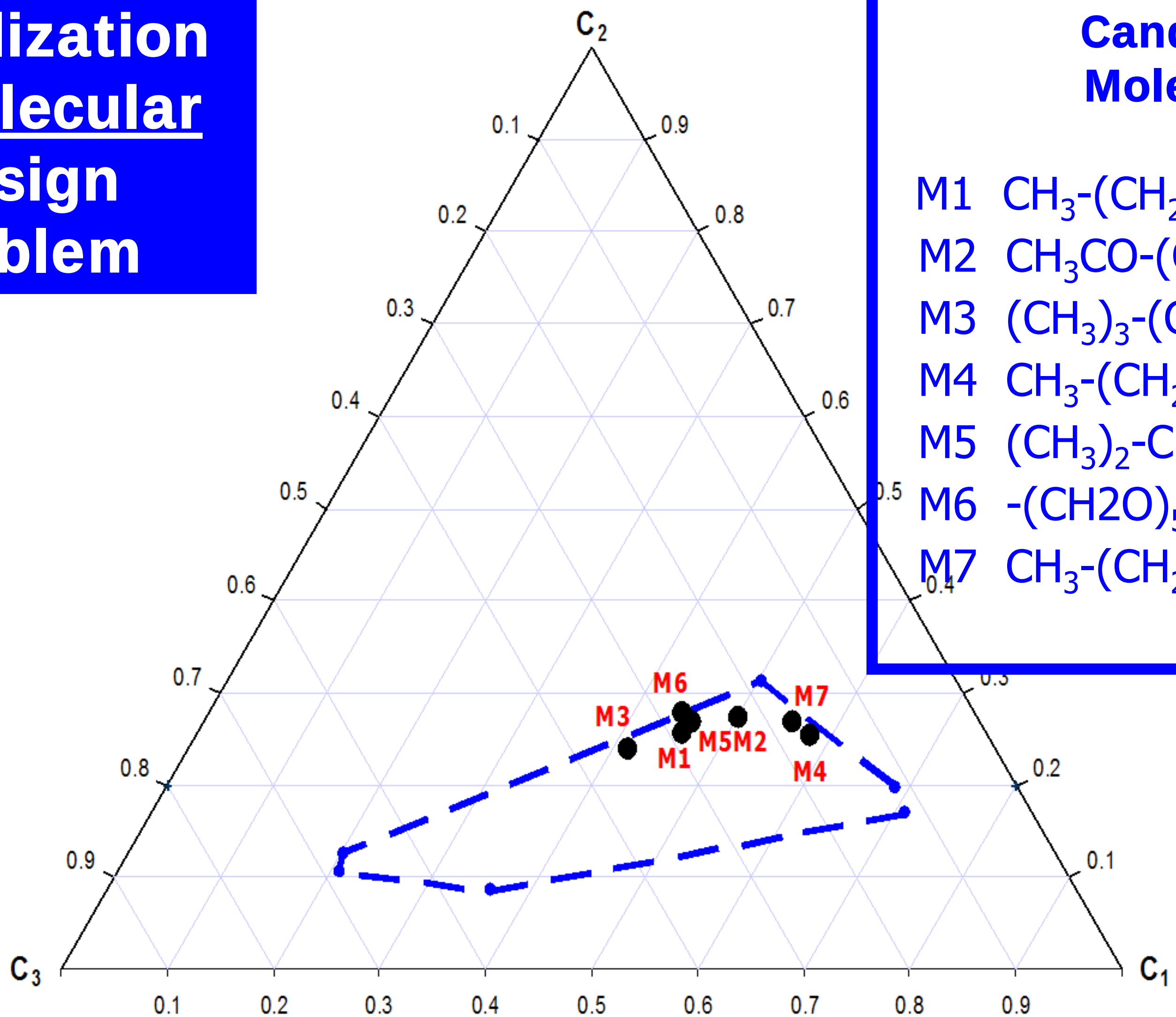


Molecular Fragments

G1: CH_3
G2: CH_2
G3: CH_2O
G4: CH_2N
G5: CH_3N
G6: CH_3CO
G7: COOH

Metal Degreasing 7:9

Visualization of <u>Molecular</u> Design Problem

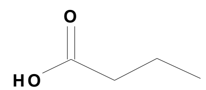


Candidate Molecules

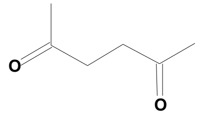
- M1 CH_3-$(CH_2)_5$-CH_3CO
- M2 CH_3CO-$(CH_2)_2$-CH_3CO
- M3 $(CH_3)_3$-$(CH_2)_5$-CH_2N
- M4 CH_3-$(CH_2)_2$-COOH
- M5 $(CH_3)_2$-CH_3CO-CCL
- M6 -$(CH2O)_5$- ring
- M7 CH_3-$(CH_2)_2$-CH_3N-COOH

Metal Degreasing 8:9

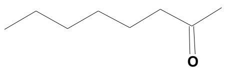
- **Formulations from Visual Design**



butanoic acid (M1)



2,5-hexadione (M2)



2-octanone (M4)

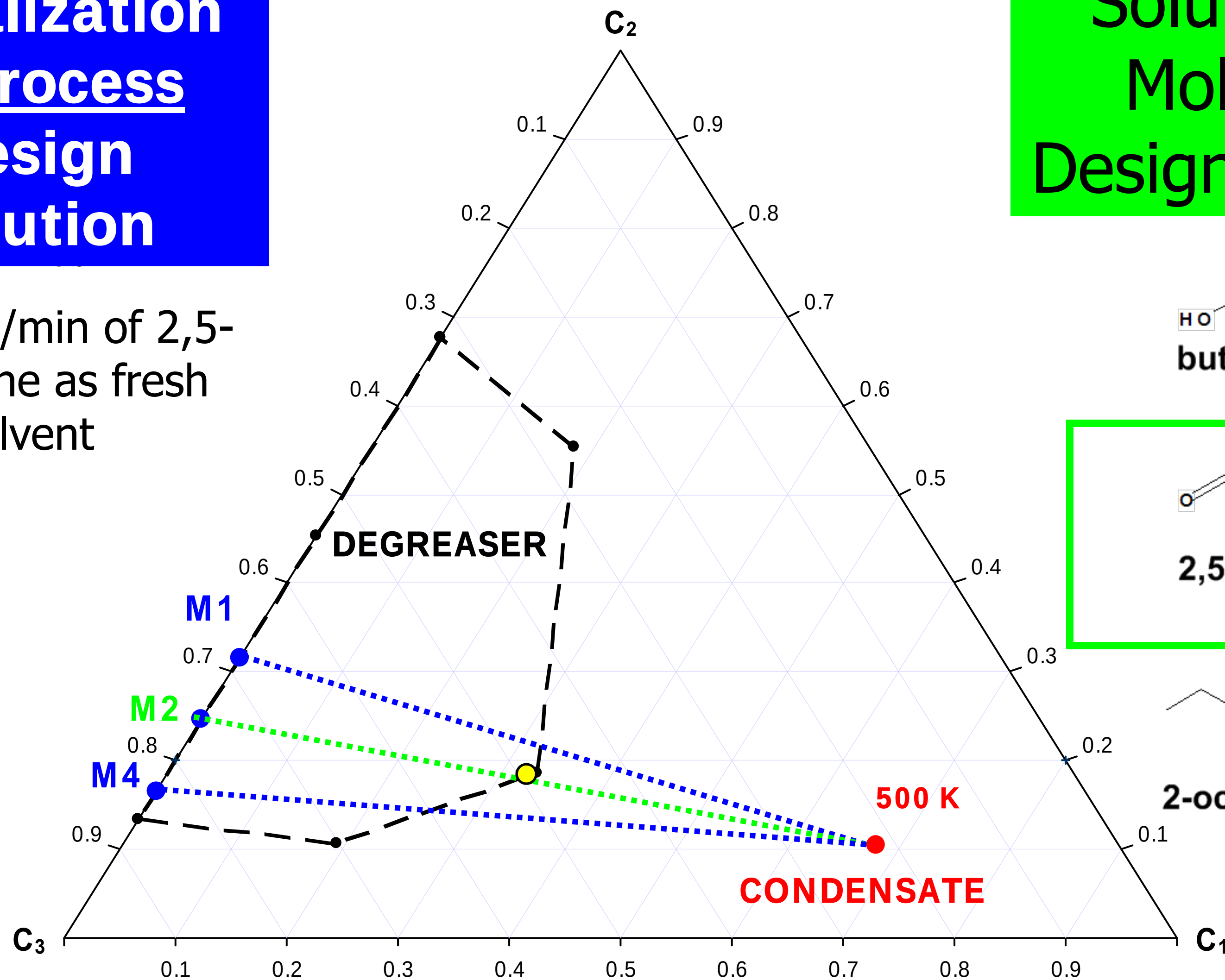
Formulation	AUP	Tb (K)	Hv (kJ/mol)	Vm (cm^3/mol)	VP (mmHg)
M1	5.06	450.58	53.19	156.85	2078.98
M2	4.71	448.54	54.13	118.03	2163.90
~~M3~~	~~5.11~~	~~437.29~~	~~49.35~~	~~189.41~~	~~2692.07~~
M4	4.86	438.97	63.29	93.39	2606.12
~~M5~~	~~4.02~~	~~413.20~~	~~43.88~~	~~121.14~~	~~4241.48~~
~~M6~~	~~4.10~~	~~428.11~~	~~44.22~~	~~127.66~~	~~3208.12~~
~~M7~~	~~5.71~~	~~485.01~~	~~70.24~~	~~112.52~~	~~1037.99~~

- **Application of Feasibility Conditions**
  - All formulations satisfy first two necessary conditions
  - M5 and M6 fail to satisfy sink AUP range
  - M3 and M7 did not match Non-GC property value
  - M1, M2 and M4 are valid solvent candidates

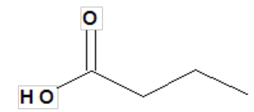
Metal Degreasing 9:9

Visualization of <u>Process</u> Design Solution

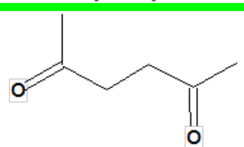
19.36 kg/min of 2,5-hexadione as fresh solvent



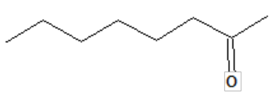
Solutions to Molecular Design Problem



butanoic acid (M1)



2,5-hexadione (M2)

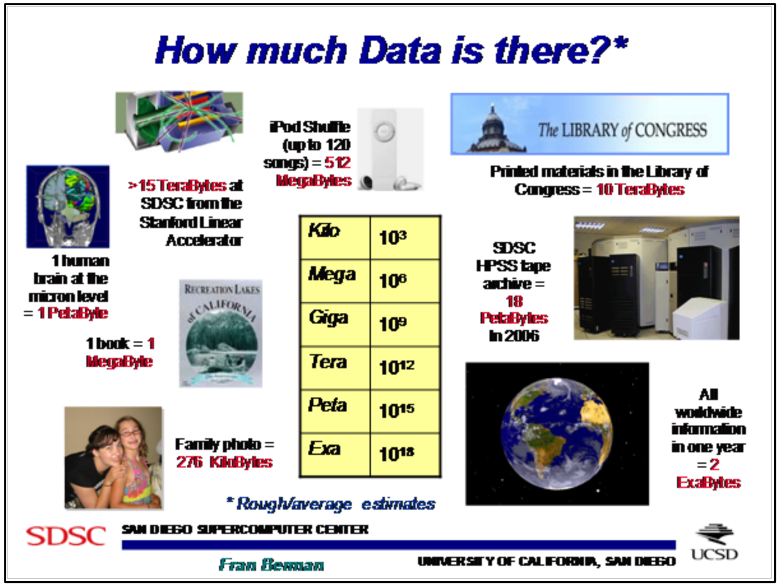


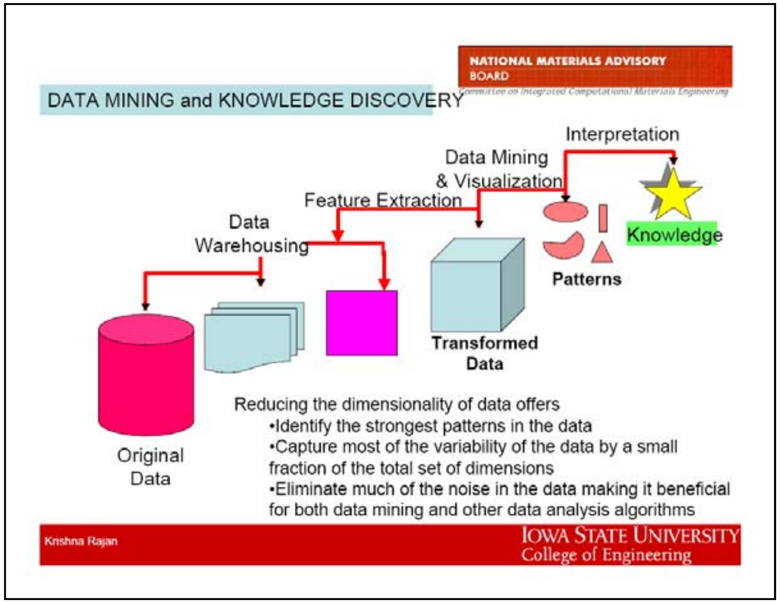
2-octanone (M4)

Product Design Challenges

National Research Council,
Committee on Integrated Computational Materials Engineering (2008)

- Strategy Execution
  - "The power of 21st century computing is making it possible to predict certain structures and properties from fundamental principles"
  - "One of the important lessons learned…is the profound importance of experimental results to calibrate and validate computational methods an fill gaps in theoretical understanding…best practiced with complimentary experimental and theoretical approaches"
  - "The properties of materials are controlled by a multitude of separate and often competing mechanisms that operate over a wide range of length and time scales…the linkage of various methods remains a great challenge"





Product Design Challenges

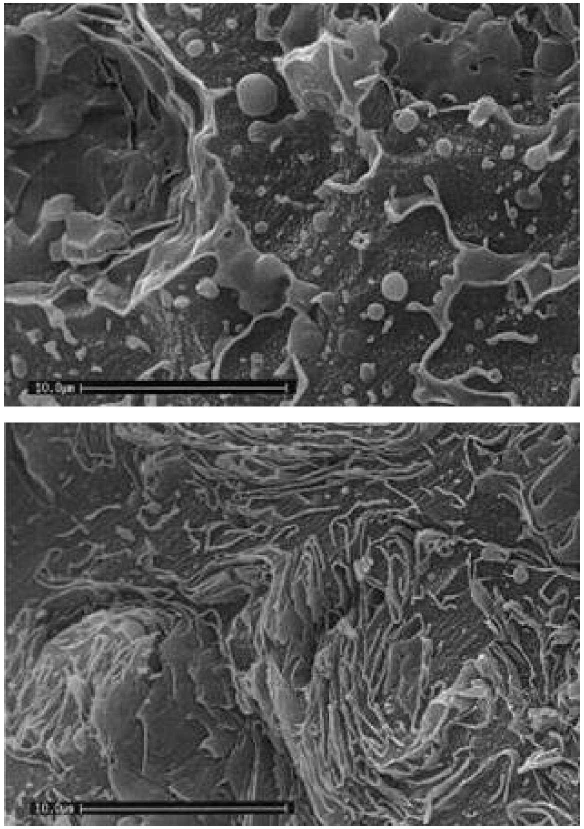
Product Design,

Michael Hill

M Hill & Associates, Inc (2005)

- Way Forward
  - Two paths: (1) “Systematic reduction of the number of alternatives through heuristics” and (2) “optimization of the set of all potential alternatives through mathematical programming”
  - “Requisite properties will be performance attributes rather than fundamental physico-chemical, or bio-chemical properties”
  - “New property estimation techniques will need to be identified and proven…since formulated products are often multi-phase structured products”
  - Methodology will “not eliminate the need for product experimentation in the laboratory, but serve to guide and focus product experimentation”

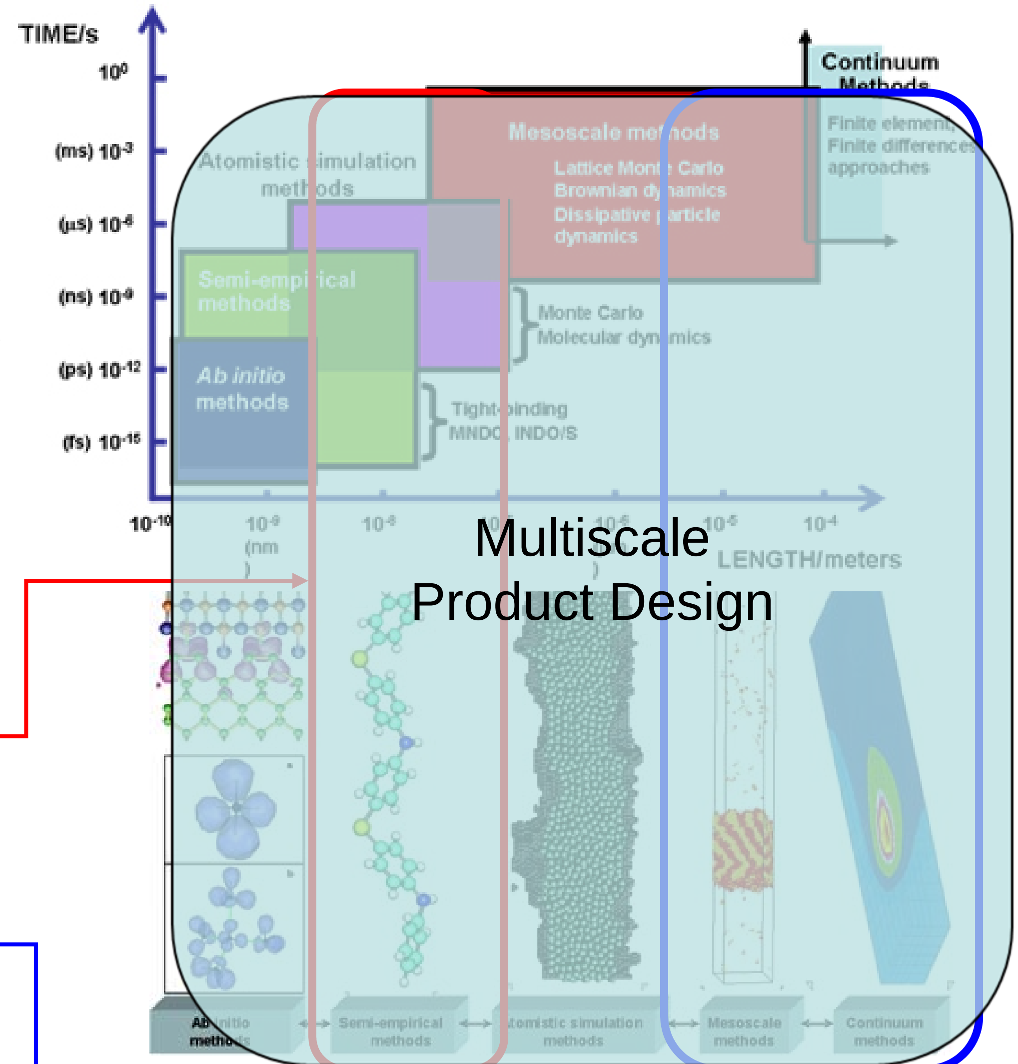
Cryo-SEM micrographs of a lamellar-structured hair conditioner manufactured under low deformation rates (top) and high deformation rates (bottom) (Edwards, 1998).



Source: M. Hill, “Product and Process Design for Structured Products”, AIChE Journal, Vol. 50, No. 8

Product Design Challenges

- **Multiscale Systems**
  - Integration of various product and process relationships so as to ensure complete solutions and global optimums
  - Utilize reverse problem formulations to generate multiple match solutions



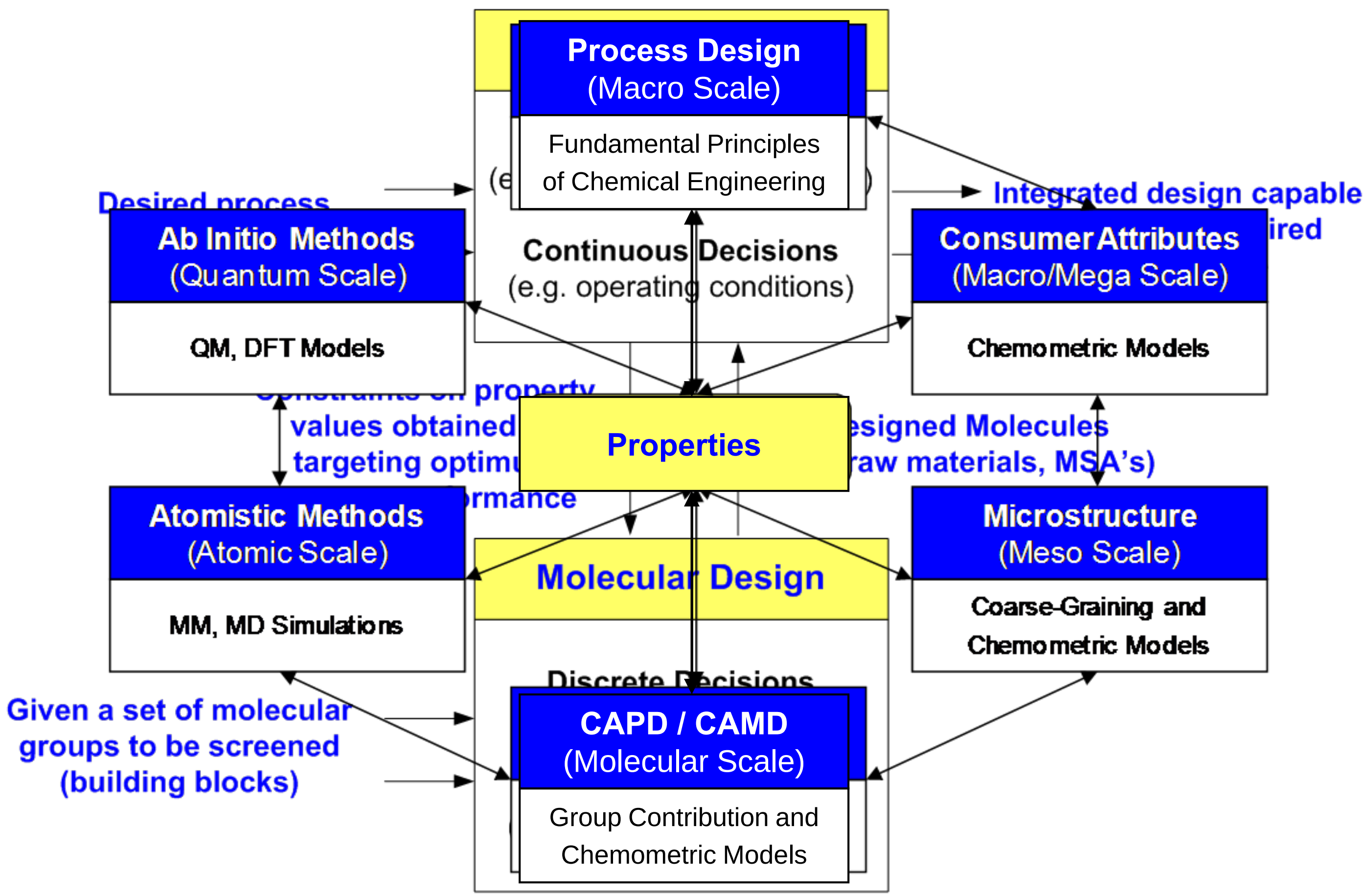
Molecular Design
(Group Contribution)

Process Design
(Fundamental Principles)

Source: Florida State University, www.eng.fsu.edu

Motivations and Challenges

Simultaneous Matching of All Scales?



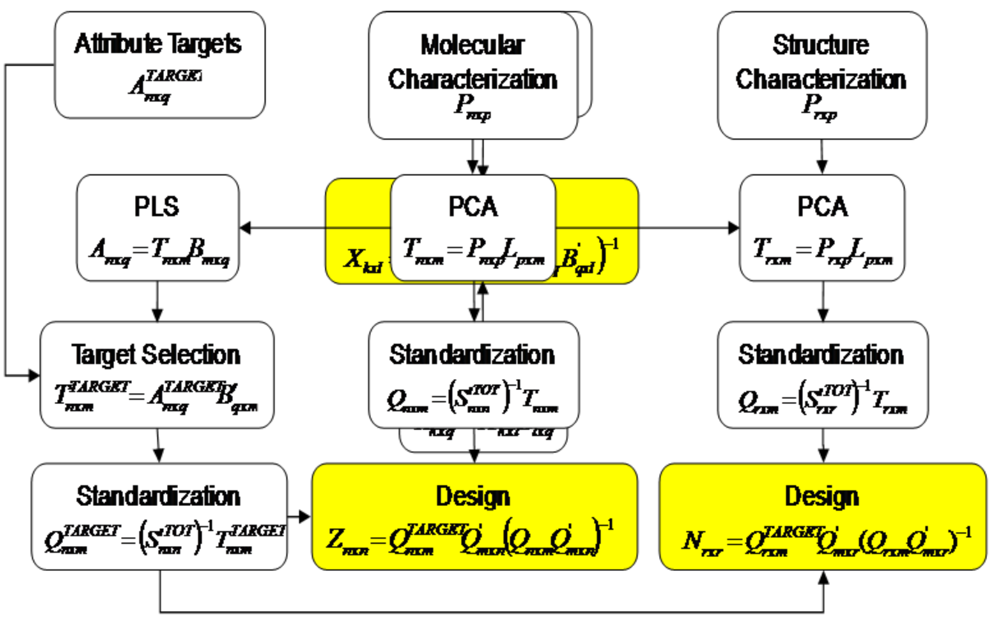
Motivations and Challenges

- Research Focus
  - Linkage of “Complimentary Experimental and Theoretical Approaches”
    - Chemometric Inference Models — **Path 1**
      - Mixture Design of Experiments (MDOE)
      - Decomposition Techniques (PCA)
      - Stochastic Simulations (Monte Carlo)
    - Semi-Empirical Models — **Path 2**
      - Higher Order Group Contribution
      - Connectivity Indices
      - Molecular Graph Theory

Methods

- Objective
  - Use a reverse problem formulation in the appropriate linearized subspace
- Method Development
  - Method includes
    1. Development of a centralized framework
    2. Development of an algorithm that chooses the appropriate properties to bridge the length scales
    3. Use of a property clustering algorithm to load descriptions into the framework and visualize the solution

Semi-Empirical Method
Empirical Method



Methods

- Empirical Method
  - Utilizes direct Attribute-Component relationship
  - Limited to selection of components only; each new molecule requires additional experimentation
  - Limited to linear correlations for global optimization
  - Subject to combinatorial explosion when developing model parameters
- Semi-Empirical Method
  - Utlizes both an Attribute-Property relationship and a Property-Component relationship
  - Enumerates all candidate molecules using molecular design techniques based on group-based indices
  - Uses linear or nonlinear correlations of attributes for global optimization
  - Less subjective to combinatorial explosion when developing model parameters

In addition, both methods also utilize Property Clustering and Chemometric Techniques

Chemometric Inference Models

- **Chemometrics**
  - "Chemometrics is the science of relating measurements made on a system or process to the state of the system or process via application of mathematical or statistical methods" – *The International Chemometrics Society (ICS)*
  - "There are techniques for collecting good data (optimization of experimental parameters, design of experiments, calibration, signal processing) and for getting information from these data (statistics, pattern recognition, modeling, structure-property-relationship estimations)" – *Wikipedia*

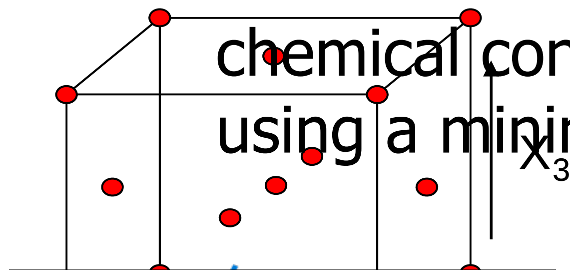
- **Focus**
  - Design of Experiments (MDOE, etc.)
  - Characterization Techniques (Spectroscopy, etc.)
  - Decomposition Techniques (PCR, etc.)

Mixture Design

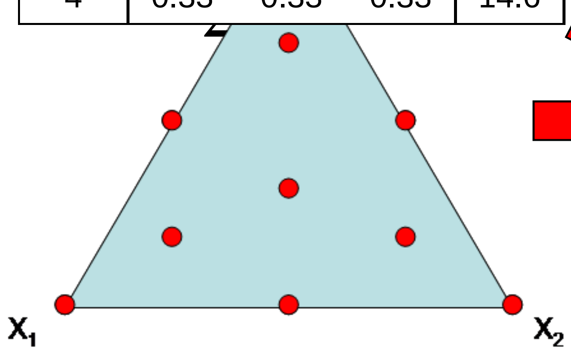
- **What is Mixture Design?**
  - Mixture Design is a Design of Experiments (DOE) tool used to determine the optimum combina chemical constituents that deliver a desi using a minimum number of experiment

Experimentation

Y = f(X)



Trial	X_1	X_2	X_3	$\hat{y}$
1	0.68	0.16	0.16	15.2
2	0.16	0.68	0.16	12.2
3	0.16	0.16	0.68	15.2
4	0.33	0.33	0.33	14.6



Interpretation / Model Selection

Polynomial

$$\hat{y} = b_o + \sum_{i=1}^{q} b_i x_i + \cdots + \in$$

$$Y = BX$$

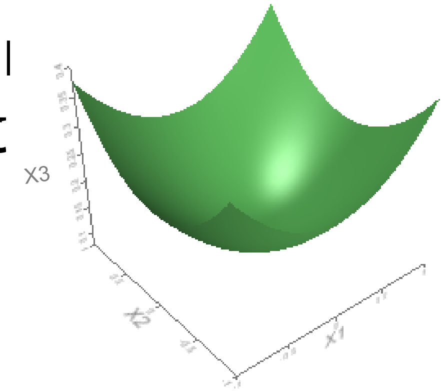
$$\boxed{B = X'Y(X'X)^{-1}}$$

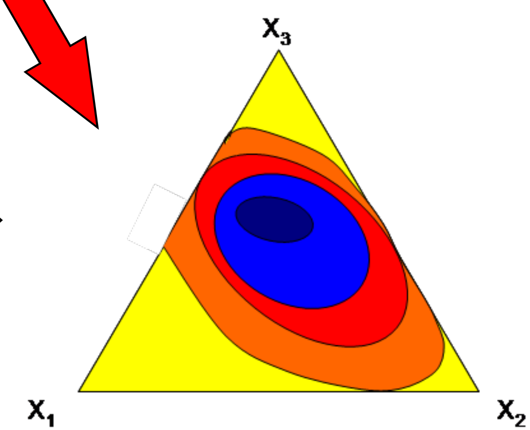
Canonical

$$\hat{y} = \sum_{i=1}^{q} b_i^* x_i + \cdots + \in$$

$$Y = B^* X$$

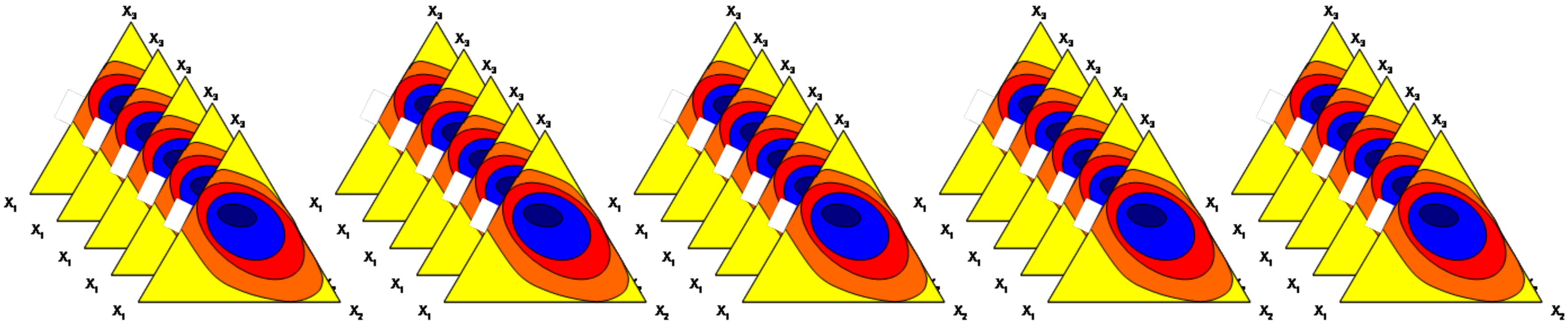
Prediction





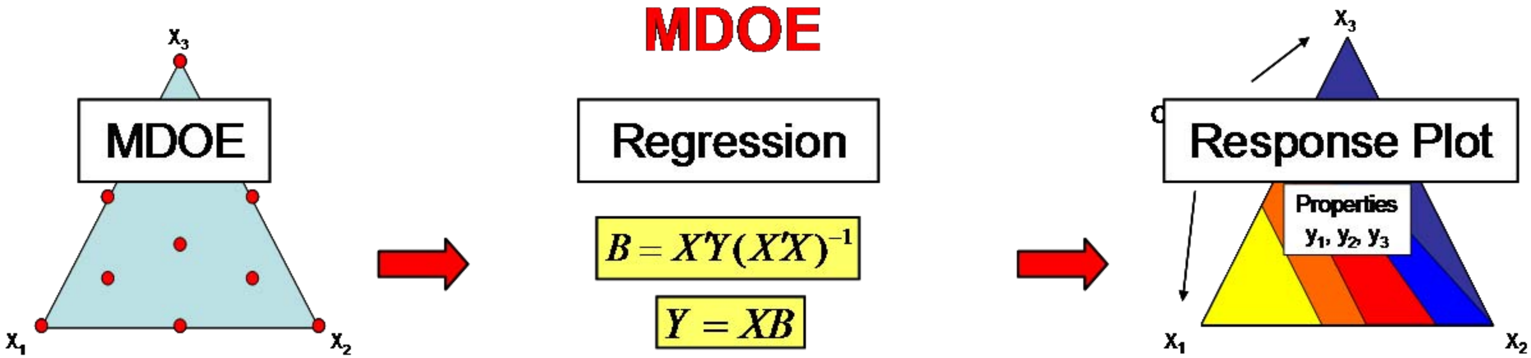
MDOE Challenges

- **Mixture Design Limitations**
  - Suffers from combinatorial problems
    - 7 components = 25 independent ternary plots per property
  - Evaluation of multiple effects is difficult



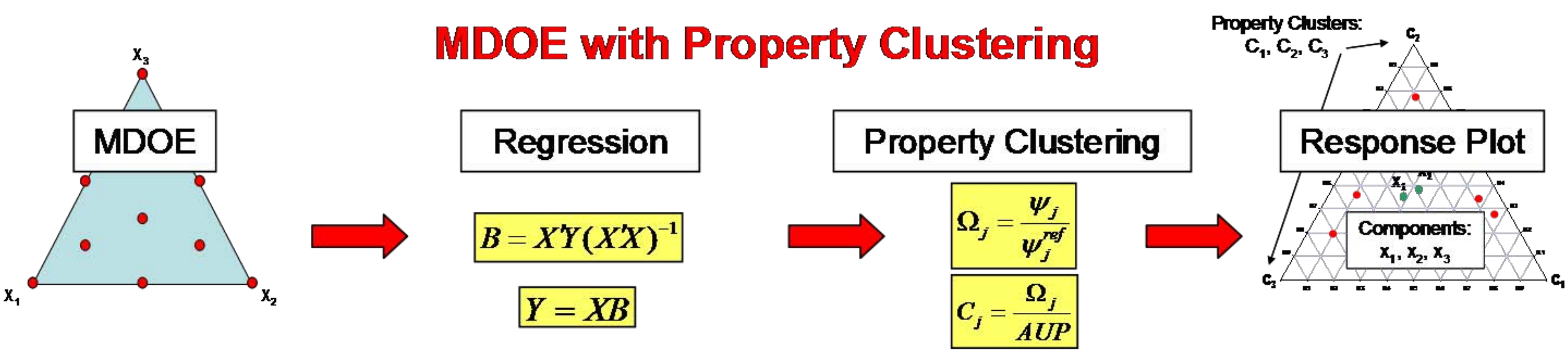
- **New method of visualizing mixture designs**
  - Must handle combinatorial intensive problems
  - Must be easy to visualize
  - Must be universal in its application

MDOE Using Property Clusters



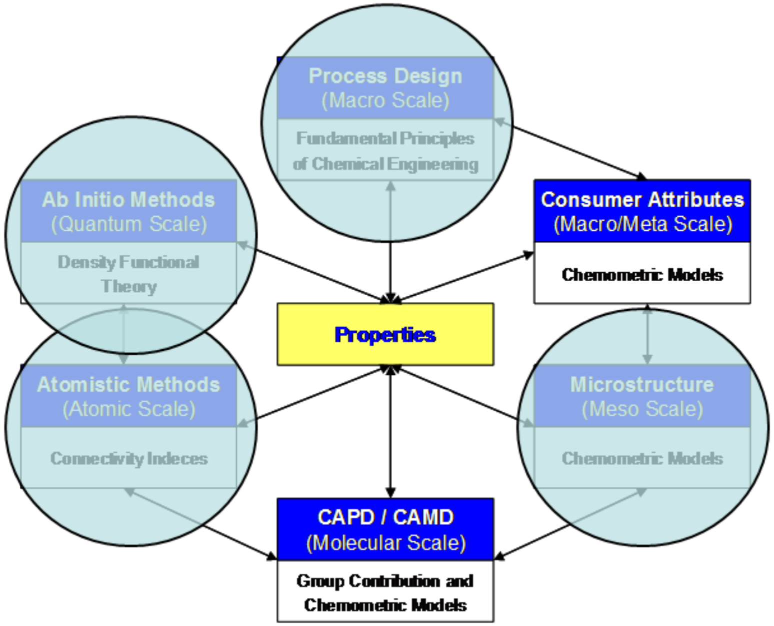
Conventional MDOE: 7 Components & 3 Properties = 75 plots

Property Clustering MDOE: 7 Components & 3 Properties = 1 plot



Example 4: Mixture Design

- **Polymer Blend Study**
  - Optimization of a polymer blend of spun yarn for use in rope for modern racing sailboats



- **Objective**
  - Optimize a ternary or smaller polymer blend to deliver the specified product attributes of high strength, low stretch, and high floatability

Polymer Blend Design 1:2

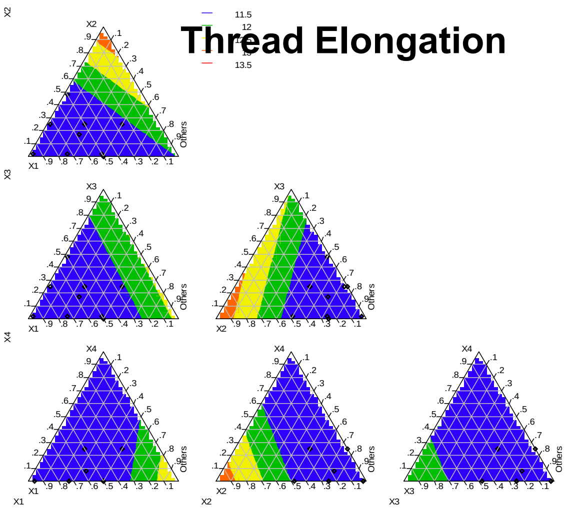
- **Attribute – Property Relationship**
  1. Strength – Knot Strength of Yarn (Cornell, 2002)
  2. Stretch – Thread Elongation (Cornell, 2002)
  3. Floatability – Specific Volume (Eden et. al, 2003)
- **Property Targets – Feasibility Range**

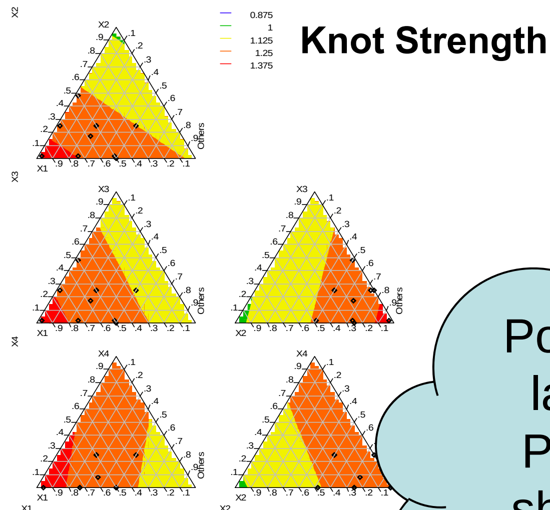
Property	Lower Bound	Upper Bound
Thread Elongation (kgf)	12.0	16.0
Knot Strength (lbf)	12.0	12.5
Specific Volume (cm3/g)	1.063	1.111

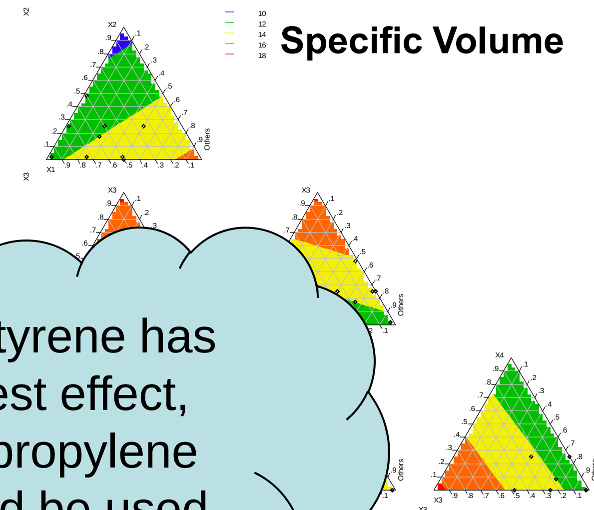
- **Polymer Candidates**
  1. LDPE
  2. Polystyrene
  3. Polypropylene
  4. Nylon 6,6

Polymer Blend Design 2:2

MDOE

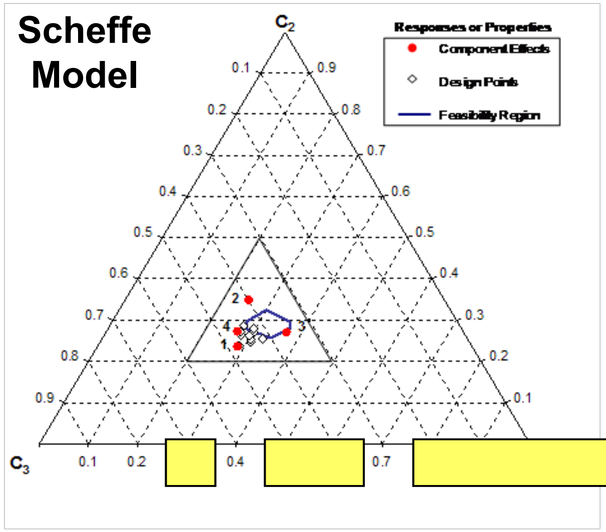


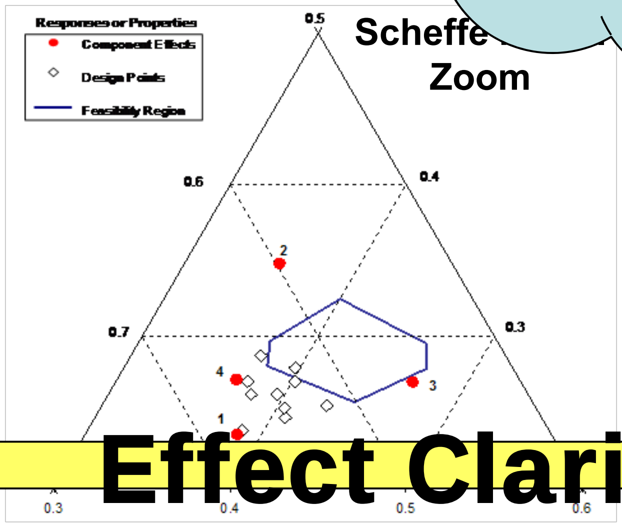


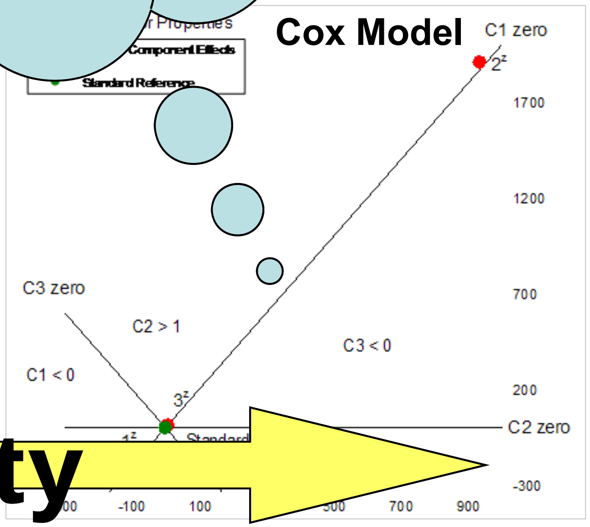


Polystyrene has largest effect, Polypropylene should be used as filler

MDOE with Proper







Effect Clarity

Case Study: Excipient Design

- Acetaminophen Tablet Design
  - "Optimization of poorly compactable drug tablets manufactured by direct compression using mixture experimental design" – Martinello *et al.*, 2006

- Objective:
  - Determine if a ternary or smaller mixture can deliver a directly compressible compact of acetaminophen

Case Study: Excipient Design

- Powder Properties
  - Angle of Repose (RA)
  - Compressibility (C)
  - Water Content (W)

Property	Lower Bound	Upper Bound
RA (deg)	0.0	30.0
C (%)	0.0	32.0
W (wt.%)	1.5	3.0

- Candidates

Excipient	Industry Name	Function
1	Microcel 102	Filler-Binder
2	Kollidon VA 64	Binder
3	Flowlac	Filler-Binder
4	Kollidon CL 30	Disintegrant
5	PEG 4000	Glidant-Lubricant
6	Aerosil 200 Pharma	Glidant-Lubricant
7	Magnesium Stearate	Lubricant

$$RA_M = \sum_{s=1}^{Ns} x_s \cdot b_s^*(RA_s)$$

$$C_M = \sum_{s=1}^{Ns} x_s \cdot b_s^*(C_s)$$

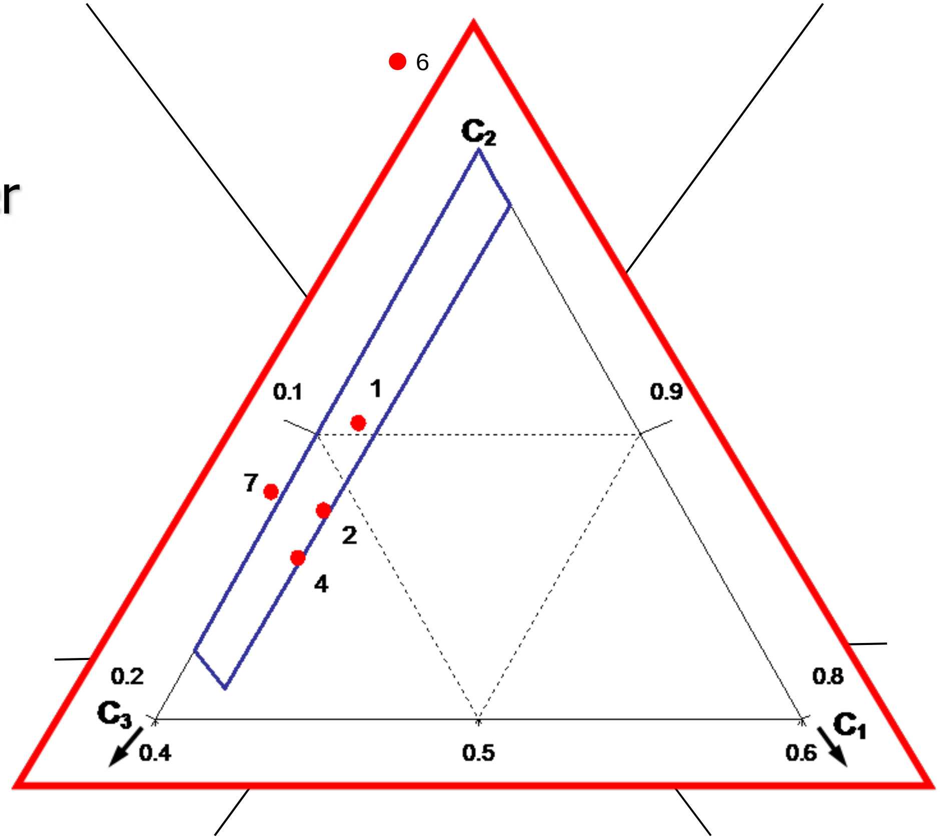
$$W_M = \sum_{s=1}^{Ns} x_s \cdot b_s^*(W_s)$$

Case Study: Excipient Design

- Constraint Check
  - Distance to real cluster space indicative of STRONG effect
  - All formulations meet all powder and tablet constraints independently

Possible Formulations

2-6	2-4-6
4-6	2-5-6
1-2-6	2-7-6
1-3-6	3-4-6
1-4-6	4-5-6
1-5-6	4-7-6
2-3-6	



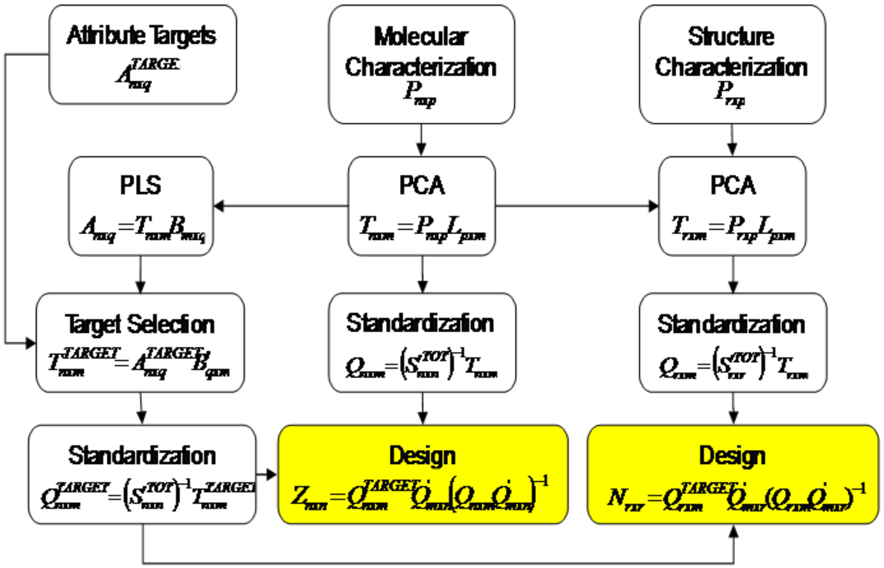
Attribute-Component Conclusions

- Attribute-Component Conclusions
  - Handles combinatorial explosion
  - Representation of combined effects of each component
  - Requires the use of negative cluster space handled by constraint AUP > 0
- Challenges
  - What about "new" molecules?
  - How to deal with secondary colinearity or nonlinearity?
  - What about "principal" properties?

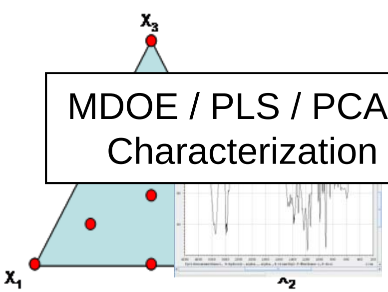
One Answer: Use Subspace Mapping w/ Latent Variable Models

Chemometrics

- **Principal Property Method**
  - DOE/PLS used to determine attribute-property relationship
  - PCA to find principal properties
  - Linearized principal property-component relationships are used to determine structure
  - Molecular design via a modified group contribution



Mixture / Molecular Design with Property Clustering



MDOE / PLS / PCA / Characterization

$A = PB$ $T = PL$

$Q = RL$

Property Models

$Qmix = RQ$

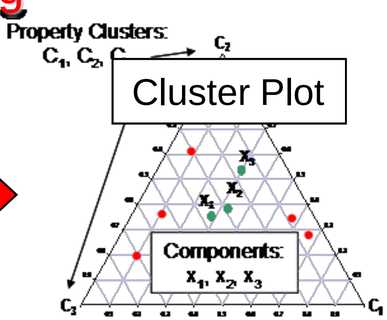
$Qmix = NgQ$

Property Clustering

$\Omega_j = \frac{\psi_j}{\psi_j^{ref}}$

$C_j = \frac{\Omega_j}{AUP}$

Cluster Plot



Summary

- **Property Clusters**
  - Provide a framework to solve property driven processes without any commitment to components.
  - Unified framework for simultaneous solution of process & molecular design problems.
  - Enables visualization and reduces problem dimensionality.
  - Maps attribute data down to subspace with orthogonal linear functions, thus ensuring global optimums and complete candidate sets are found

Future Directions

- **Property Clusters**
  - Expand property description options through molecular signature and characterization techniques
  - Integrate topological indices with group contribution based flowsheet design
  - Include microstructure information via crystallinity algorithms, both deterministic and stochastic
  - Analyze the proper information pathways through ontology, network component analysis, and other algorithms

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  - Charles Solvason & Nishanth Chemmangattuvalappil

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